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The TRAM flap for breast reconstruction

Studies on perioperative cutaneous blood flow,
vasoconstriction, and indices of obesity

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Academic Dissertation

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To my family

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Abstract

In Finland breast reconstruction is performed for about 10–15 % of women operated on for breast cancer. A popular method for creating a new breast is the transverse rectus abdominis musculocutaneous (TRAM) flap formed solely of the patient's own tissue from the lower abdominal area. The flap can be raised as a pedicled or a free flap. The pedicled TRAM flap, based on its nondominant pedicle superior epigastric artery (SEA), is rotated to the chest so that blood flow through SEA continues. The free TRAM flap, based on the dominant pedicle deep inferior epigastric artery (DIEA), is detached from the abdomen, transferred to the chest, and DIEA and vein are anastomosed to recipient vessels on the chest. Cutaneous necrosis is seen in 5–60 % of the pedicled TRAM flaps and in 0–15 % of free TRAM flaps.

The aim of this study was to measure changes in cutaneous blood flow on the ipsilateral (over the rectus muscle) and contralateral (opposite side) sides of the flap with laser Doppler flowmetry (LDF) and transcutaneous oxygen tension ($P_{tc}O_2$) at different phases before, during and after breast reconstruction with pedicled (I) and free (II) TRAM flaps, and to predict development of necrosis in pedicled TRAM flaps. The role of plasma endothelin-1 (ET-1), a powerful vasoconstrictor secreted by vascular endothelial cells, in cutaneous necrosis of flaps and the peripheral vasoconstriction observed after long operations (III), and the effect of felodipine, a vasodilating calcium antagonist, on those parameters (IV) were also studied. One aim was to study the association of cutaneous or fat necrosis and the amount of obesity of the patient, using body mass index (BMI), waist-hip circumference ratio (WHCR) and thickness of subcutaneous abdominal fat as indices of obesity (V).

This thesis consists of five prospective studies (I–V) performed in altogether 58 women, ten of whom took part in studies III and V. In

14 pedicled TRAM flaps (I), elevation of the contralateral side of the flap caused an increase in cutaneous blood flow on the ipsilateral side of the flap compared to the measurements taken after induction of anesthesia. A possible cause for the hyperemia may be opening up of the “choke” vessels interconnecting adjacent vascular areas, angiosomes. Ligation of DIEA caused a significant decrease of LDF levels on the contralateral skin, lasting until the first postoperative day. The contralateral $P_{tc}O_2$ decreased from the initial 48 ± 3 mmHg to 5 ± 2 mmHg when DIEA was cut and stayed low on the operation day. It increased slowly during the postoperative week. The LDF and $P_{tc}O_2$ levels were lower on the contralateral than ipsilateral side of the flap at all measuring times. SEA apparently cannot perfuse the pedicled TRAM flap sufficiently on the operation day.

In ten free TRAM flaps (II), elevation of the contralateral side caused a similar hyperemia as in pedicled flaps. Interruption of blood flow before performing the anastomoses was seen as a decrease of LDF levels. LDF levels and the ipsilateral $P_{tc}O_2$ returned to the base line levels in the recovery room, as did the contralateral $P_{tc}O_2$ on the third postoperative day. Compared with the pedicled flaps in study I, the postoperative blood flow in the free TRAM flap seems generous.

Cutaneous necrosis was observed in eight (57 %) of the 14 pedicled TRAM flaps (I). The development of cutaneous necrosis could be predicted based on intraoperative LDF measurements. The contralateral LDF level decreased after ligation of the DIEA to a lower level in flaps developing necrosis (43 ± 7 % of the initial value) compared to flaps healing uneventfully (74 ± 7 %, $p < 0.01$). Cutaneous necrosis cannot be predicted based on the intraoperative $P_{tc}O_2$ values. The contralateral $P_{tc}O_2$ was significantly lower in the recovery room and on the postoperative days in flaps developing necrosis (I).

In study III, plasma ET-1 concentrations were elevated preoperatively, 8.9 (5.5–12.5) pg/ml (median, 25–75 quartiles), near 3 pg/ml during the operation, and around 5 pg/ml during the postoperative recovery room period of three hours in nine patients with a pedicled TRAM flap. Temperature gradient (T_{grad} , the difference between skin temperatures of the antebrachium and index finger) indicated peripheral vasoconstriction preoperatively and postoperatively. A statistically significant nonlinear correlation was found in the nonparametric Spearman rank correlation test between ET-1 and T_{grad} ($r = 0.32$, $p < 0.01$), and ET-1 and mean arterial pressure (MAP) ($r = 0.25$, $p < 0.05$), but not between ET-1 or T_{grad} and development of necrosis, and ET-1 and heart rate (HR). ET-1 may play a role in postoperative peripheral vasoconstriction after long operations (III).

Oral felodipine (5 mg) administered on the preoperative evening and on the operation morning, caused no differences in perioperative plasma ET-1 concentrations, T_{grad} , postoperative $P_{tc}O_2$, or development of cutaneous

necrosis of free TRAM flaps between the felodipine group ($n = 10$) and the control group ($n = 10$) in a placebo-controlled randomized study. An increase of HR was seen in felodipine patients. (IV).

Cutaneous or fat necrosis was observed in two of the five overweight patients ($BMI > 25$), in three of the six patients of ideal weight, but not in the one underweight patient ($BMI < 19$). None of the 12 patients were obese ($BMI > 30$). Four of the six patients with lower body type fat distribution ($WHCR < 0.80$), none of the four patients with upper body type fat distribution and one of the two patients with $WHCR 0.80-0.84$ developed necrosis. There were no differences in the thickness of subcutaneous fat in patients with and without necrosis. Neither BMI nor the thickness of abdominal subcutaneous fat seems to be associated with the development of cutaneous or fat necrosis in pedicled TRAM flaps. An association may exist between lower body type fat distribution and development of marginal necrosis in pedicled TRAM flaps (V).

List of original publications

This thesis is based on the following original publications, referred to in the text by their Roman numerals:

- I Tuominen HP, Asko-Seljavaara S, Svartling NE, Härmä MA. Cutaneous blood flow in the TRAM flap. *Br J Plast Surg* 1992; 45: 261–269.
- II Tuominen HP, Asko-Seljavaara S, Svartling NE. Cutaneous blood flow in the free TRAM flap. *Br J Plast Surg* 1993; 46: 665–669.
- III Tuominen HP, Svartling NE, Tikkanen IT, Saijonmaa O, Asko-Seljavaara S. Perioperative plasma endothelin-1 concentrations and vasoconstriction during prolonged plastic surgical procedures. *Br J Anaesth* 1995; 74: 661–666.
- IV Tuominen HP, Svartling NE, Tikkanen IT, Asko-Seljavaara S. The effect of felodipine on endothelin-1 levels, peripheral vasoconstriction and flap survival during microvascular breast reconstruction. *Br J Plast Surg* 1997; 50: 624–631.
- V Tuominen HP, Kinnunen J, Svartling NE, Asko-Seljavaara S. Indices of obesity and behaviour of the pedicled TRAM flap in breast reconstruction. *Scand J Plast Reconstr Surg Hand Surg* 1997; 31: 333–338.

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Abbreviations

ACE	angiotensin-converting enzyme	NIRS	near-infrared spectroscopy
BCT	breast-conserving therapy	PaO ₂	arterial oxygen tension
BMI	body mass index (kg/m ²)	P _{tc} O ₂	transcutaneous oxygen tension
CI	confidence interval	SD	standard deviation
DBR	delayed breast reconstruction	SEA	superior epigastric artery
DCIS	ductal carcinoma in situ	SEM	standard error of mean
DIEP	deep inferior epigastric perforator	SIEA	superficial inferior epigastric artery
ET	endothelin	T _{ant}	temperature of antebrachium skin
ET-1	endothelin-1	T _{grad}	temperature gradient (T _{ant} –T _{ind})
GAP	gluteal artery perforator	T _{ind}	temperature of index finger
HR	heart rate	T _{periph}	peripheral temperature
IBR	immediate breast reconstruction	T _{rect}	rectal temperature
LCIS	lobular carcinoma in situ	TAP	thoracodorsal artery perforator
LD	latissimus dorsi	TRAM	transverse rectus abdominis musculocutaneous
LDF	laser Doppler flowmetry	WHCR	waist-hip circumference ratio
LDPI	laser Doppler perfusion imaging	WHO	World Health Organization
MAP	mean arterial pressure		

1 Introduction

Breast cancer is the most common cancer in women. In 1989–1993, it was diagnosed annually in 67 women per 100 000 in Finland, in 2004 in 86 women, and by the year 2015 the figure is expected to reach 117 (Finnish Cancer Registry 2007). Despite the increasing incidence, the prognosis has improved during the last couple of decades, with approximately 80 % of the patients being alive five years after the diagnosis (Finnish Cancer Organizations 2006).

Chemotherapy and radiation therapy along with surgery, either conserving or radical, form the cornerstone of breast cancer treatment (National Cancer Institute 2008a). Mastectomy is performed in about half of patients. In patients undergoing mastectomy, disturbances in body image and problems with the exogenous prosthesis can lead to a variety of psychological problems, physical symptoms, and difficulties in social life. Nowadays, either immediate or delayed breast reconstruction with an artificial implant or autologous tissue is offered in many cases to improve the quality of life (Blamey 1998, Newman 1999, Piasecki 2006).

The disadvantages related to the prosthesis can be avoided, and the esthetic result is often considered better with breast reconstruction using autologous tissue. Transplantation of either a pedicled or a free transverse rectus abdominis musculocutaneous (TRAM) flap for breast reconstruction was introduced some 30 years ago (Robbins 1979, Holmström 1979, Hartrampf 1982). The breast created with the TRAM flap is soft and natural-looking compared to other methods. Regardless of the popularity of the TRAM flap, complications related to the flap circulation still occur.

To overcome the technical obstacles of breast reconstruction, it is of the utmost importance to understand the changes in cutaneous blood flow of the flaps during and after surgery. Vasoconstriction can compromise the viability of the flap. During operations of long duration, imminent hypothermia results in decreased cutaneous blood flow. An important mediator in vasoconstriction is endothelin, ET-1, a peptide secreted by vascular endothelial cells (Yanagisawa 1988). High ET-1 levels have been measured in ischemic experimental flaps (Matsuzaki 1993). The untoward effects can be antagonized with such drugs as calcium antagonists, which have been shown to suppress ET-1 release (Kiowsky 1991, Liu 1994) and also to enhance the survival of experimental skin flaps (Yessenow 1991, Davis 1999).

Overweight of the patient may pose a risk to the viability of the TRAM flap. The probable underlying causes are vascular problems (Lapidus 1984) and the stretch caused by the heavy flap on musculocutaneous perforator vessels nourishing the flap (Scheflan 1984). Consequently, obesity has been considered a relative contraindication to breast reconstruction by some authors (Scheflan 1983a, Hartrampf 1987, Grotting 1994). However, the effects of the type of body fat distribution and the thickness of abdominal subcutaneous fat on survival of the flap skin are unknown.

This thesis was designed to evaluate the changes in cutaneous blood flow in the TRAM flaps and to study the effects of a calcium antagonist, felodipine, on plasma endothelin concentrations and flap survival. Moreover, the effects of indices of obesity on TRAM flaps were assessed.

2 Review of the literature

2.1. Breast cancer

2.1.1. Incidence

Breast cancer is the most common malignant tumor in women in Finland, accounting for 31 % of all female cancer cases. The incidence of breast cancer has been increasing since the 1980s. It was diagnosed in Finland annually in 2664 women during 1989–1993, representing 67 per 100 000 women, and in 3770 women in 2003, representing 86 per 100 000 women (Finnish Cancer Registry 2007). The incidence is at the same level in all Western countries (Mäkelä 2006). The probable causes of the increase are trends towards obesity, changes in reproductive patterns, and the use of postmenopausal hormone replacement therapy (American Cancer Society 2006). Thanks to better diagnostics by mammography, more cancer cases are observed at an early stage. According to the latest trends in Finland, 5250 of the 15 000 new cancer cases diagnosed in 2015 in women are expected to be breast cancer cases (Finnish Cancer Organizations 2006).

Every tenth woman living until the age of 90 years has been calculated to get breast cancer during their lifetime. Very few cases occur in women younger than 25 years. In Finland, about 25 % of cases are diagnosed in the age group 25–49 years, 25 % in the age group 50–59 years, and 50 % in patients aged 60 years or over (Finnish Cancer Registry 2007). The incidence increases with advancing age. In USA, in women aged 20–24 years the incidence rate was low, 1.3 cases per 100 000, while the corresponding rate was 497 per 100 000 in women aged 75–79 during 1998–2002 (American Cancer Society 2006).

2.1.2. Manifestations

The female breast consists of 15–20 lobules attached by connective tissue and fat. The lobules are connected by small ducti (World Health Organization 1981, American Joint Committee of Cancer 2002, Finnish Current Care Guidelines 2007).

The most common form of breast cancer is ductal carcinoma. It occurs as an invasive form or as ductal carcinoma in situ (DCIS). The ductal invasive carcinoma represents 75–80 % of all invasive breast cancers. DCIS is an early, precancerous condition, where the cancer cells have not invaded the breast tissue, but remain inside the ducti. DCIS usually remains local, but may sometimes progress to invasive cancer. The incidence of DCIS has increased considerably because of increased detection by mammography. In USA, DCIS accounted for 3 % of all breast cancers diagnosed in 1973 and 14 % in 1995 (Page 1982, Ernster 2000). The less common lobular carcinoma (10–15 % of all breast cancers) originates from the lobules and is often bilateral. Lobular carcinoma in situ (LCIS) also exists; it is not considered malignant, but is a risk factor for breast cancer. It is usually multicentric and frequently bilateral. Paget's disease is a form of breast cancer manifesting as eczema of the nipple. In histological examination, intraepidermal carcinoma cells, DCIS changes, and sometimes invasive growth are observed. There are also some less common cancer types, e.g. tubular, mucinous, papillary, scirrhous, and inflammatory breast cancers (National Cancer Institute 2008a).

2.1.3. Treatment

Treatment of breast cancer should be tailored individually for each patient. Breast cancer is commonly treated by various combinations of surgery, radiation therapy, chemotherapy,

hormone therapy, and monoclonal antibody therapy. It is a multidisciplinary team approach, involving specialists in surgery, radiology, pathology, oncology, nuclear medicine, plastic surgery, and anesthesiology. Selection of therapy may be influenced by the age, menopausal status, general condition and opinion of the patient, stage of the disease, histologic and nuclear grade of the primary tumor, estrogen-receptor and progesterone-receptor status, measures of proliferative capacity, and HER2/neu gene amplification (Finnish Current Care Guidelines 2007, National Cancer Institute 2008a).

The basic objectives of the treatment are to remove the tumor from the breast and the metastases from the axilla, nowadays with the help of sentinel node biopsy, and to minimize the recurrence of the cancer locally and in the axilla. Selection of the surgical method is based on the pTNM classification and staging of the tumor (American Joint Committee of Cancer 2002, Finnish Current Care Guidelines 2007). The operation methods used are mastectomy or breast-conserving therapy (BCT). Simple or total mastectomy includes removal of the entire breast. In modified radical mastectomy, also the lymph nodes in the axilla are removed. Radical mastectomy, including also removal of the underlying chest wall muscle, is rarely used today because of proven effectiveness of the less disfiguring surgeries (Veronesi 2002). The indications for mastectomy are shown in Table I (Finnish Current Care Guidelines 2007, National Cancer Institute 2008a).

During the last ten years, skin-sparing mastectomy has become popular. It involves removal of the nipple/areolar complex and preserving the breast's skin envelope (Simmons 2003). It is considered safe in selected T1/T2 tumors (Toth 1991, Cunnick 2004). In

BCT, the tumor is removed by lumpectomy, quadrantectomy, or segmental mastectomy. Nowadays in Finland, BCT is used in 50–60 % of breast cancer operations. Mastectomy is performed for 40–50 % of the women, i. e. 1500–1850 women yearly (Stakes 2007). The most important prognostic marker in breast cancer is the status of the axillary lymph nodes (Fisher 1983, Morrow 1996). The use of sentinel node biopsy has decreased the need for unnecessary axillary evacuations, which can cause sequelae for the patient (Ververs 2001), and scarring or damage of the vessels used as recipients in microvascular breast reconstruction. The lymph node nearest the site of the primary cancer, receiving the lymph drainage directly from the tumor, is regarded as the sentinel node, the most likely site of early metastases (Morton 1992). In this procedure technetium-labeled sulfur colloid solution, vital blue dye, or both are injected around the tumor or biopsy cavity preoperatively, and the lymph node or nodes first activated by the marker solution or the dye (sentinel nodes) are removed for histological examination as a frozen section analysis. If the sentinel nodes are free of cancer, the axilla is left intact. If a metastasis is found, and in rare cases where sentinel nodes are not found, the axilla is evacuated in the same operation. Short follow-up studies have revealed hardly any axillary recurrence in patients who were left without axillary evacuation because of negative sentinel nodes (Schrenk 2001, Chung 2002, Guenther 2003, Veronesi 2003, Leikola 2006). However, no long-term follow-up studies exist on sentinel node biopsy since it has only been in use from the end of the 1990s onwards. In Finland, it has been in use since 2000.

The local recurrence rate is increased in BCT compared with mastectomy in patients

Table I. Indications for mastectomy.

1. Tumor is large compared with the size of the breast, and neoadjuvant therapy is not planned.
2. Cases with multiple areas of cancer far from each other in the breast.
3. Inflammatory breast cancer after chemotherapy.
4. Cases where wound margins free of cancer cannot be produced by breast conserving therapy.
5. Cases where the adjuvant therapy being planned cannot be given.
6. The patient wishes mastectomy to be performed.

not receiving radiation therapy (Cutuli 2000). Adding radiation therapy to the regimen after BCT increases long-term survival to the same level as in patients with mastectomy (Cutuli 2000). Radiation therapy is used to reduce the size of the tumor or metastases before surgery or to destroy cancer cells remaining in the breast, chest wall, or axilla after surgery (Early Breast Cancer Trialists' Collaborative Group 2000). Most patients with DCIS can be treated with BCT with or without radiation therapy. Tamoxifen may decrease local invasive recurrence in DCIS, but it has no effect on survival (Fisher 1999). The side-effects of tamoxifen include an increased risk of thrombotic events and endometrial cancer (Fisher 1999). It is not recommended in routine therapy, but some patient groups may benefit from it (Finnish Current Care Guidelines 2007, National Cancer Institute 2008a).

All histologic types of invasive breast cancer may be treated with BCT and radiation therapy (Weiss 1992). In patients without distant metastases (stages I–III A + operable III C patients) (American Joint Committee of Cancer 2002), options for surgical management of the primary tumor include BCT plus radiation therapy, mastectomy plus reconstruction, and mastectomy alone. Survival is equivalent with any of these options, as documented in randomized prospective trials (Jacobson 1995, Veronesi 1995, van Dongen 2000, Veronesi 2002).

Most women with LCIS can be managed without additional local therapy after biopsy. No evidence indicates that re-excision to obtain clear margins is required. Tamoxifen has decreased the risk of developing breast cancer in women with LCIS (Fisher 1998). It is included in the therapy guidelines of LCIS patients in USA (National Cancer Institute 2008a), but in Finland it is not routinely used in this patient group (Finnish Current Care Guidelines 2007). At present there is no curative treatment for disseminated breast cancer, but the quality of life can be improved and the disease-free and total survival increased with systemic therapy. Breast cancer metastases are frequently osseal, but they are often found also in the liver, brain, lungs, and other soft tissues. Systemic therapy

includes chemotherapy, hormone therapy, and biological therapy.

Systemic treatment can be given preoperatively as neoadjuvant therapy in order to shrink the tumor, making the operation possible. Neoadjuvant therapy has been found to be as effective as postoperative therapy in terms of survival, disease progression and distant recurrence (Mauri 2005). Adjuvant systemic treatment given after surgery as different combinations of cytotoxic drugs has proven effective in reducing recurrence and death rates, and the effect can last more than 15 years after the treatment (Hortobagyi 1998, Early Breast Cancer Trialists' Collaborative Group 2005). It is given to patients with a high risk of recurrence and also to women with metastatic breast cancer when curative surgery is not possible. Hormone therapy has been observed to be effective in reducing recurrence and death rates in both premenopausal and postmenopausal women with hormone receptor-positive tumors (Early Breast Cancer Trialists' Collaborative Group 1998, 2005). The most commonly used antiestrogen drug is tamoxifen. Recently, aromatase inhibitors have been approved for use in postmenopausal women as the initial hormone therapy or after tamoxifen (Winer 2005). The monoclonal antibody trastuzumab, which targets the HER2/neu protein of breast tumors, has been effective in increasing survival in women with metastatic breast cancer (Cobleigh 1999, Slamon 2001, Vogel 2002). Data also show that women taking trastuzumab in addition to chemotherapy have a reduced recurrence of cancer compared with women receiving chemotherapy alone (Hampton 2005, Romond 2005).

2.1.4. Prognosis

The majority of patients are cured permanently. Nowadays, about 88 % of patients are alive 5 years after the diagnosis, 80 % after 10 years, 71 % after 15 years, and 63 % after 20 years (Ries 2005). The prognosis was worse in 1990; in USA, 78 % of the patients whose cancer was diagnosed five years earlier were alive, and only 65 % ten years after the diag-

nosis. (National Cancer Institute 2008b). The five-year relative survival rate is slightly lower in the youngest age groups; 82 % of patients younger than 40 years are alive five years after the diagnosis, compared with 89 % of patients aged 40–74 years or 88 % of those older than 75 years (American Cancer Society 2006). The most important factor affecting survival is the stage of the disease. The risk for recurrence in an early stage (I) is 10–30 % during ten years after the diagnosis and 40–50 % in stage II during five years after the diagnosis. Eighty-five percent of the recurrences occur within the first five years, but recurrence can occur even 10–20 years after the diagnosis.

Although the incidence of breast cancer continues to increase, mortality has been decreasing, principally as a result of earlier diagnosis and improvements in adjuvant systemic therapy. This means that increasingly more women with breast cancer treated years ago are living a full life, most of them without recurrence or metastases.

2.2. Breast reconstruction

2.2.1. Indications

The indications for breast reconstruction are loss of the breast because of surgery or absence or deformity of the breast for congenital or acquired reasons. This thesis deals with breast reconstruction after mastectomy for breast cancer.

Patients who have had or are expected to have considerable asymmetry of the breast after tumor ablative surgery are suitable candidates for breast reconstruction. Most breast reconstructions are performed on patients undergoing a mastectomy. It is recommended that these patients should be counselled about reconstructive options before their tumor surgery (Blamey 1998). Women with locally advanced disease may also be suitable candidates for breast reconstruction (Newman 1999). In the preoperative evaluation, aspects taken into account are disease status, future treatment plans, surgical history, and other health problems, volume of the contralateral breast, body habitus, the patient's expectations (Piasecki

2006), and the availability and skills of the surgical team.

Breast reconstruction is considered only if this is the patient's wish. After mastectomy, many women find the external prosthesis very uncomfortable, and also experience physical and psychological disturbances in their body image. The wish for breast reconstruction is strongly related to age and working status. An estimated 80 % of mastectomized patients younger than 45 years wish to have reconstructive surgery, while the corresponding figure for women over 65 years is only 2 % (Korvenoja 1998).

Today, about 210 000 invasive breast cancers are diagnosed yearly in USA, and approximately 35 % of these patients will have breast reconstruction (Jemal 2005). In Finland, of the 3770 women diagnosed annually with breast cancer, mastectomy is performed on about 40–50 %, i. e. on 1500–1885 women. Breast reconstruction is performed on about 75 % of women younger than 50 years. Thus, annually, some 500–700 patients undergo reconstructive surgery after breast cancer in Finland (Stakes 2007).

Relative contraindications for the procedure are metastatic disease or severe medical comorbidities, e.g. massive obesity or marked cardiopulmonary problems.

2.2.2. Principles of breast reconstruction

In mastectomy, varying amounts of skin, breast tissue, and often the nipple-areola complex are removed. In traditional mastectomy, the amount of skin excised is quite large, while skin sparing mastectomy leaves most of the breast skin intact. The aim of breast reconstruction is to produce an optimal esthetic result by restoring the volume, shape, softness, contour, and skin of the breast, using the opposite breast as a reference point. If the other breast is excessively large, its reduction may be needed. In such cases, the reductioplasty of the opposite breast and the breast reconstruction are performed during the same procedure, with the aim of producing breasts as symmetric as possible.

Breast reconstruction can be performed at

the time of mastectomy (immediate breast reconstruction, IBR) or at a later stage, months or years after mastectomy (delayed breast reconstruction, DBR) (Cunningham 1986, Feller 1986, Hang-Fu 1991). The timing of the reconstruction is considered by a multidisciplinary team consisting of surgeons and oncologists, and it depends on the patient's preferences, the stage of the disease and the need for adjuvant therapy (Curtin 2004).

Breast reconstruction has traditionally been carried out as a delayed procedure, but nowadays IBR has become the method of choice in many hospitals. IBR is ideal for patients with an early disease, stages I or II. It is considered oncologically safe in most cases, and has not caused a delay in chemotherapy or radiotherapy according to the literature (Mustonen 2004, Gouy 2005). In Helsinki University Central Hospital, IBR is recommended for patients requiring mastectomy for diffuse DCIS, for patients with inherited susceptibility for breast cancer, for local recurrence after conservative surgery, or when mastectomy is needed because of multifocality or large size of the cancer (Jahkola 2003). DBR is considered a safer alternative if the patient is expected to receive oncological treatment for an invasive cancer. IBR could cause a delay in the start of chemo- or radiotherapy when there are problems in wound healing (Jahkola 2003, Pomahac 2006). Compared with DBR, the esthetic result of IBR is often better because the skin envelope and the inframammary fold are maintained (Kroll 1995), and also the cost of the treatment is reduced because of one operation instead of two (Khoo 1998). After successful IBR, it may be easier for the patient to manage with the psy-

chological stress caused by loss of the breast (Rosenqvist 1996, Al-Ghazal 2000). The breast mass can be restored and the breast contour recreated with nonautologous breast reconstruction by inserting an artificial implant, with autologous breast reconstruction using the patient's own tissue to reform the breast, or with a combination of these methods. Selecting the type of reconstruction depends on the patient's comorbidities, previous surgical history, body habitus, and the possibility of pregnancies in the future. Autologous breast reconstruction is recommended for patients generally healthy except for the breast cancer (Tachi 2005). If the patient is a heavy smoker or has severe comorbidities affecting the microcirculation, such as diabetes, cardiovascular diseases, or coagulation tendency, a nonautologous reconstruction or no reconstruction is often recommended.

Some characteristics of different types of breast reconstructions are shown in Table II.

2.2.3. Nonautologous breast reconstruction

The simplest breast reconstruction technique is to place a breast implant subcutaneously or under the pectoralis major muscle. The implant is a bag filled with silicone or saline, and it can be of fixed or adjustable volume. If the breast tumor has been operated on using a skin sparing technique, a prosthesis of fixed volume can be used. There are various types of implants with different forms and surfaces. Fixed volume implants are suitable for selected patients, when the desired volume of the reconstructed breast is small. They are also used to give additional volume in connection with an autologous

Table II. Some characteristics of the main types of breast reconstructions.

Type of breast reconstruction	Nonautologous (implant)	Autologous (LD flap)	Autologous (pedicled TRAM flap)	Autologous (free TRAM flap)
Duration of operation	1–2 hours	3–4 hours	3–6 hours	4–6 hours
Need of surgical teams	1 (1 surgeon + 1 instrument nurse)	1	2	2
Microsurgical experience needed	no	no	sometimes	yes
Length of hospital stay	2–3 days	3–4 days	5–7 days	5–7 days

reconstruction, e.g. the latissimus dorsi flap (Ahmed 2005). The lengths of operation and hospital stay are shorter in nonautologous than autologous reconstructions. Earlier, a high incidence of flap necroses, wound dehiscence, implant extrusions, and peri-implant contractions has been reported after subcutaneous application of a silicone breast implant because of insufficient overlying skin to cover the subcutaneously placed prosthesis after mastectomy (Watts 1976, Vandamme 1985).

Nowadays a nonautologous breast reconstruction is performed in many centers in two phases with an expander prosthesis (Agha-Mohammadi 2006). First, a tissue expander is placed under the pectoralis muscle. This is an empty silicone bag, which is gradually over a few weeks inflated with saline, in an outpatient setting, to stretch the overlying tissue. Some months later, in a second operation, the expander is removed and replaced with an implant. The second operation can be avoided by using a Becker-type expandable prosthesis, which has a remote injection port. When the expander is fully inflated, the injection port is removed and the prosthesis left in place (Becker 1987). The expander technique for breast reconstruction is suitable for women with a relative lack of skin after mastectomy and small nonptotic breasts (Ahmed 2005). It is a good method also for young women with bilateral prophylactic mastectomies, for whom a bilateral TRAM flap reconstruction is not a good option because of future pregnancies (Jahkola 2003).

The most common complication associated with breast implants is capsule contracture, resulting in a firm and spherical breast, breast asymmetry, and possible implant displacement (Tachi 2005). The capsulated prosthesis must sometimes be removed and a new reconstruction made, causing increasing costs and inconvenience for the patient. Capsular contracture commonly develops after post-reconstruction radiotherapy (Spear 2001). The safety of silicone in breast implants has been discussed widely. Some leakage is thought to occur in most implants because of degradation of the outer layer (Tachi 2005). The association between silicone implants and increased risk of

connective tissue diseases has thus far not been confirmed (Janowsky 2000).

2.2.4. Autologous breast reconstruction

The problems arising from breast reconstructions with an implant provided the motivation to develop new methods for breast reconstruction without any foreign material. The first report of an autologous breast reconstruction was published in 1966 (De Cholnoky 1966). Breast reconstruction with the patient's own, autologous tissue is considered the optimal method for creating a natural-looking and -feeling breast. Autologous breast reconstruction consists of taking a flap of tissue from a donor site and transferring it to the site of the removed breast. The autologous flaps for breast reconstruction are often obtained from the lower abdomen or the upper back and sometimes the gluteal region. Traditionally, the flap has consisted of muscle and the overlying fascia, subcutis, and skin accompanied by the vessels nourishing these tissues. Factors affecting the selection of the tissue for reconstruction include the amount of tissue needed and the amount of tissue available at the donor site. The wishes and lifestyle of the patient are also considered when choosing the flap (Jahkola 2003). Although the surgical procedure is complex and time-consuming, the result of a ptotic, soft, symmetrical reconstructed breast is usually better than the result achieved with nonautologous reconstruction. Moreover, the implant-related complications are usually avoided. Autologous flaps for breast reconstruction tolerate postoperative radiation therapy well (Zimmermann 1998, Pomahac 2006).

The flap can be transferred as a pedicled or free flap or a combination of these two methods. A pedicled flap is dissected from its surroundings and turned to the recipient site so that it remains attached to its original blood vessels. The use of the pedicled latissimus dorsi (LD) musculocutaneous flap from the patient's upper back was described for breast reconstruction by Schneider with coworkers in 1977 (Schneider 1977). It is a reliable flap with

a good blood supply. It is a popular method for breast reconstruction for women with fairly small breasts. The additional scars on the back and the usually required breast implant or expander, with the possibility of capsular contracture, may limit its use (Tachi 2005). In 1979, Robbins published the original description of the successful use of a vertical superiorly based rectus abdominis musculocutaneous flap for breast reconstruction in four women (Robbins 1979). Hartrampf and colleagues published in 1982 anatomical and clinical studies of the lower abdominal pedicled TRAM flap for breast reconstruction (Hartrampf 1982). The lower TRAM flap with its variations is the current gold standard of autologous breast reconstruction (Grotting 2003, Piasecki 2006, Serletti 2006). The pedicled and free TRAM flaps with their subtypes are described in detail later in the text. The TRAM flap has many advantages compared with other methods for autologous breast reconstruction. The new soft and natural-looking breast can be created in one surgical procedure, it is easier to produce symmetry with the other breast, the patients are usually happy to get rid of unwanted excess abdominal fat tissue, and the scars of the operation are well concealed (Grotting 2003, Serletti 2006). The result of TRAM flap reconstruction is shown in Figure 1.

Usually, only one of the rectus muscles is used for unilateral breast reconstruction to limit any postoperative problems to the abdominal wall. Choosing which one of the rectus

muscles is used depends on the type of TRAM flap reconstruction, the amount of tissue needed, and the shape of the other breast (Schefflan 1983b, Hartrampf 1987, Chang 2000b, Serletti 2006). When the TRAM flap is unavailable because of extensive scars after lower abdominal operations or the patient is exceptionally thin or very obese (Tachi 2005, Jähkölä 2003), the pedicled flaps used are usually the LD flap, the thoracodorsal artery-perforator flap (TAP) (Angrigiani 1995), or the lateral thoracodorsal flap (Holmström 2002).

When transferring a free flap, the flap is elevated from its original position, its pedicle vessels are dissected, their proximal ends are ligated, and then the pedicle vessels are cut. The flap is then lifted to its final destination, which has been prepared for the transfer, and the pedicle vessels are anastomosed to the recipient blood vessels near the mastectomy area with a microsurgical technique. The use of a free TRAM flap for breast reconstruction was first reported by Holmström in 1979 (Holmström 1979) and later popularised by Grotting (Grotting 1989). To avoid problems caused by harvesting part of the rectus abdominis muscle, newer modifications of the free TRAM flap have been created, including the deep inferior epigastric perforator flap (DIEP) (Koshima 1989, Allen 1994) and the superficial inferior epigastric artery (SIEA) flap (Arnez 1999). These flaps consist of skin and subcutaneous tissue with the nourishing vessels, leaving the rectus muscle in place. When these modifications of the free TRAM flap are unavailable or unusable, the superior or inferior gluteal free flaps (Shaw 1983, Paletta 1989), the gluteal perforator free flap (GAP) (Blondeel 1999), the lateral transverse free thigh flap (Elliott 1990), the free laparoscopically harvested omental flap (Cothier-Savey 2001, Jimenez 2002), and the Rubens flap (Hartrampf 1994, Elliott 1998), among others may be suitable.

In Finland most of the breast reconstructions are performed with the LD flap with or without an implant, or with the TRAM flap and its modifications. The different types of breast reconstruction performed at the Department of Plastic Surgery, Helsinki University Central Hospital, in 2007 are presented in Table III.

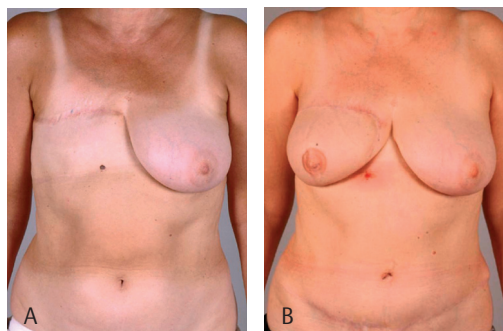


Figure 1. Result of breast reconstruction with a TRAM flap. The same patient before (A) and after (B) the operation.

2.2.5. The TRAM flap

Pedicled TRAM flap

The technique for breast reconstruction with a pedicled TRAM flap has not changed essentially from the procedure described by Hartrampf and colleagues in 1982 (Hartrampf 1982, Hartrampf 1987, Grotting 2003, Serletti 2006). The pedicled TRAM flap is a good option for breast reconstruction in patients who are generally healthy nonsmokers, of normal weight or only moderately obese, and have suitable tissue in the lower abdomen (Serletti 2006).

The flap is formed of a transverse elliptiform skin island raised from the lower abdominal area, mostly below the umbilicus, with the underlying subcutaneous fat and the rectus abdominis muscle (whole or its medial two-thirds) with its vessel pedicle. Usually the muscle opposite to the mastectomy side is chosen. The operation is performed under general anesthesia. Stable hemodynamics and mild hypervolemic hemodilution are maintained during the operation and postoperatively, and a decrease of temperature is prevented, as recommended for microvascular operations (Robins 1983, Macdonald 1985, Sigurdsson 1995). The operation is usually performed by two microsurgically experienced teams. The principles of this operation are outlined in Figure 2. The preselected skin island, about 20 cm in width and 8–14 cm in height, is dissected from its surroundings. The distal half of the skin-subcutis island, contralateral to the muscle side, is first elevated from the abdominal wall fascia as far as to the linea alba. The ipsilateral half of the skin flap, lying over the rectus muscle, is then dissected, leaving three medial centimeters of the anterior rectus sheath on the flap. The two rows of musculocutaneous perforators run through this strip of the rectus sheath. The

rectus abdominis muscle is then cut above the arcuate line. At this stage, the flap has a double circulation through the inferior and superior epigastric vessels. The inferior epigastric vessels are then cut, and the flap, which is now perfused by the superior epigastric vessels, is tunnelled under the upper abdominal skin and subcutis to the mastectomy area. The breast is shaped by rotating the flap 180° so that the medial side of the reconstructed breast represents the contralateral side of the flap. The distal portion of the contralateral side skin (zone IV, see Section 2.3.4.) is discarded. During the operations presented in this thesis, the abdominal wall was reconstructed without mesh using nonabsorbable continuous sutures to the fascia. Nowadays, the defect in the abdominal fascia is usually repaired with synthetic mesh (Serletti 2006).

Free TRAM flap

The use of a free TRAM flap for breast reconstruction was first reported by Holmström in 1979 (Holmström 1979). After the studies of Grotting and coworkers (Grotting 1989) suggesting better blood flow in the free than the pedicled TRAM flap, the free flap has gradually exceeded the pedicled flap in popularity (Tachi 2005, Serletti 2006). The free TRAM flap is thought to be more reliable than the pedicled TRAM flap in smokers, in patients with previous abdominal scars, and in patients with marked obesity, diabetes, hypertension, or other diseases affecting the microcirculation (Tachi 2005, Serletti 2006).

The principles of this operation are shown in Figure 2. The skin-subcutis island of the free TRAM flap is raised in the same way as with the pedicled TRAM flap. A small area (length about 2,5 cm, width 1,5–2 cm) of the anterior rectus fascia containing the medial

Table III. The different methods used for breast reconstructions performed after mastectomy for patients with breast cancer at the Department of Plastic Surgery, Helsinki University Central Hospital in 2007.

Pedicled TRAM flap	(Pedicled) LD flap	Free TRAM flap	(Free) DIEP flap	(Free) SIEA flap	Other autologous free flaps	Non-autologous	Total
0	40	24	17	3	5	2	91

and lateral perforators overlying the fascia is incised. Under the fascia, a 5-cm portion of the rectus abdominis muscle extending from the level below the umbilicus to the arcuate line is prepared to be taken within the flap. A lateral narrow strip of the innervated rectus muscle is left in place to avoid contraction of the muscle edges. Today, a medial strip of the muscle is also left in place; this is believed to help maintain the abdominal muscle tonus. At this stage, the recipient vessels in the mastectomy area are prepared. At the time of the studies in this thesis, the thoracodorsal or the scapular circumflex vessels were used as recipient vessels in our hospital. Later on it has been stated that if an axillary node dissection has been or is being performed the thoracodorsal vessels are to be used as the recipient vessels of the flap. For patients with total mastectomy without axillary node dissection or with sentinel node biopsy only, the internal mammary vessels are preferred (Dupin 1996, Serletti 1999). When the appropriate vessels have been dissected in the thoracic area, the inferior epigastric vessels are dissected down to their origin from the external iliac vessels, part of the rectus muscle is cut at both ends, and the superior epigastric vessels are ligated and cut. The inferior epigastric vessel pedicle is then divided and clamped, and the flap lifted to the chest. The pedicle vessels are anastomosed end-to-end with a microsurgical technique to the recipient vessels, usually the vein first. After completing

the anastomoses, the abdominal wall is closed by nonabsorbable sutures, nowadays with the help of inlay mesh when needed. The neobreast is designed, situating the former umbilical area caudally and the contralateral side of the flap medially. Excessive or nonviable skin and subcutis of the flap, especially in zone IV, is removed at the closing phase.

Other variants of the TRAM flap

Many modifications and refinements have been made to the TRAM flap to ensure sufficient blood flow to the reconstructed breast and to diminish donor-site morbidity. The *bipedicled TRAM flap* is based on the traditional skin-subcutis island and both of the rectus muscles with their superior epigastric pedicles. It is expected that blood flow provided by both of the superior pedicles is better than blood flow through a traditional pedicled TRAM flap. The bipedicled flap is used when additional flap tissue is needed for creating a large neobreast for a woman with a limited amount of abdominal tissue, and for patients with lower abdominal midline scarring. One of the major disadvantages of a bipedicled flap is the increase in donor-site morbidity (Ishii 1985, Wagner 1991, Simon 2004).

One way to try to enhance the TRAM flap blood flow is to create an *augmented* or *"supercharged"* TRAM flap. In this procedure the inferior epigastric, superficial epigastric, or superficial circumflex iliac vessels of the ipsi-

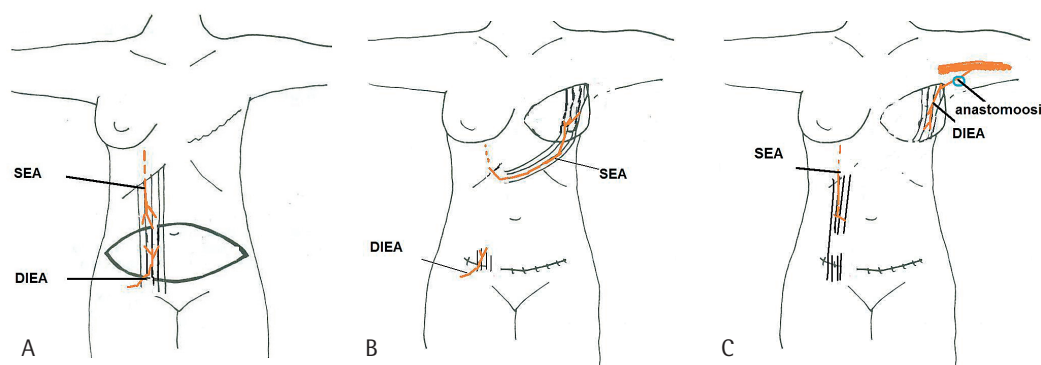


Figure 2. Principles of breast reconstruction. The preoperative situation is presented in Fig. 2 A, the pedicled TRAM flap in Fig. 2 B and the free TRAM flap in Fig. 2 C. The superior epigastric artery (SEA) and the deep inferior epigastric artery (DIEA) are marked in the pictures.

lateral or contralateral side of a conventional pedicled TRAM flap are anastomosed to recipient vessels in the axilla (Harashina 1987, Schefflan 1988). A “recharged” TRAM flap has also been developed, where the ipsilateral (muscle side) deep inferior epigastric vessels of a pedicled TRAM flap are anastomosed to the deep inferior vessels of the contralateral side (skin-subcutis island) of the flap (Berrino 1994). Attempts to improve venous outflow from the pedicled TRAM flap have been made by anastomosing veins of the ipsilateral or contralateral side to veins in the axillary area (Barnett 1996, Yanaga 1999).

To decrease the disadvantages caused by harvesting the rectus muscle, minimal amounts of the rectus muscle can be included in a free TRAM flap, thus being called the *muscle-sparing free TRAM flap*. After the 1990s, perforator flaps have become popular in reconstructive surgery. The DIEP flap is a free flap formed of the same skin-subcutis island as the TRAM flap. It is based on the perforator vessels originating from the inferior epigastric vasculature (Koshima 1989, Allen 1994). Only a small amount of the muscle and anterior rectus fascia around the perforator is enclosed within the flap. The flap is attached to the mastectomy site in the same way as the free TRAM flap. The frequency of using DIEP flaps is on the rise, as surgeons become more comfortable with the meticulous operation technique.

The *SIEA flap* is also used as a free flap for breast reconstruction (Grotting 1991, Arnez 1999). It consists of a skin-subcutis island from the lower abdomen, based on the superficial inferior epigastric vessel pedicle. The muscle and fascia remain completely intact during the procedure, which is the main advantage of this method. The superficial inferior epigastric artery arises from the femoral artery, about 1 cm below the inguinal ligament, and turns upward in front of the inguinal ligament. The SIEA flap can be used only if an adequate SIEA is present. It is not found in about half of the patients, and in many patients the vessel caliber is too small (Chevray 2004).

2.2.6. Surgical complications of the TRAM flap

Surgical complications and total flap loss

Postoperative infections and hematomas are rare in breast reconstructions with the TRAM flap (Serletti 2006). The most common surgical complications are problems related to the abdominal donor site, the overlying mastectomy skin, or the flap itself. Early abdominal wall complications include seroma formation and delayed healing of the abdominal incision, sometimes leading to necrosis of the umbilicus or the abdominal skin. The most common late abdominal wall complications are laxity, hernia, and chronic pain (Blondeel 1997, Reece 1998, Nahabedian 2002a). To decrease abdominal wall complications, medial and lateral portions of the rectus muscle can be left in place during pedicled and free TRAM flap elevations and a synthetic mesh can be used for closure of the abdominal wound.

After undermining, the mastectomy skin area sometimes heals slowly and part of the skin may be lost. This is considered to be due to inadequate resection of compromised skin during mastectomy. The slow healing can delay the onset of chemotherapy after immediate breast reconstruction in some cases (Serletti 2006).

The most important and serious complications related to the TRAM flap are total or partial loss of the flap. Total flap loss is the result of irreversible cessation of blood flow in the flap, usually leading to failure of the breast reconstruction. Flap ischemia can occur because of arterial thrombosis, venous thrombosis, or the flap being too large for its intrinsic blood supply (Kerrigan 1994). Typical rates of postoperative thrombosis lie between 2 % and 5 % (Serletti 2006). In pedicled flaps, thrombosis is usually due to a microcirculatory low-flow state caused by improper flap design, ischemia-reperfusion injury, systemic factors (hypotension, sepsis, vasoconstrictors or smoking), or local compression of the pedicle or the flap (Vedder 2005). Sufficient reduction of venous blood flow can produce flap necrosis in spite of adequate arterial flow (Fujino 1967). In free flaps, the flap failure is usually caused by thrombosis

of the pedicle artery or vein at the site of the microvascular anastomosis. Venous occlusion is more common than arterial occlusion in free flaps, leading to total flap loss if not treated in time (Vedder 2005). Venous or arterial occlusion is speculated to be a consequence of poor surgical technique, leaving adventitia or media of the vessel exposed to blood-carrying fibrin and platelets (Vedder 2005). Kinking or external compression of the artery or vein can also be the stimulus leading to occlusion of the vessel. Patients with a hypercoagulable tendency may be at risk for flap failure. It might be useful to preoperatively measure blood levels of some markers for coagulation and fibrinolysis (Ols-son 2001). Flap salvage is often successful with immediate return to the operating room. The incidence of total flap loss is usually less than 1 % in pedicled flaps and between 0 % and 5 % in free flaps (Table IV).

The learning curve of a complex procedure affects the rate of complications. In a retrospective series of 185 breast reconstructions with free TRAM flaps during 1990-1995, the overall complication rate was 50 % among the first 50

patients, but decreased to 20–25 % in the rest of the patients, probably because of the team getting experience on the procedure routines (Nieminen 1999).

Cutaneous and fat necrosis in the TRAM flap

Partial flap loss is observed as cutaneous or fat necrosis. It is the result of locally inadequate blood flow, which can be caused by, for instance, vasoconstriction of the small arterioles or too low perfusion pressure in the distal cutaneous and subcutaneous areas of the flap (Vedder 2005).

Cutaneous necrosis of the flap develops early, within a few days to weeks after the operation. It is seen clinically as dark edges of the TRAM flap, with no signs of local blood flow. It is usually treated with dressing changes and in some cases with surgical revision. Cutaneous necrosis often lengthens the hospital stay and costs, and exposes the patient to additional operations. A TRAM flap with cutaneous necrosis is shown in Figure 3. Fat necrosis is a form of partial flap loss. It results in a firm mass

Table IV. Incidence of total or partial flap loss in pedicled and free TRAM flaps.

Study	TRAM flap type	Number of flaps	Total flap loss (%)	Partial flap loss (%)	Fat necrosis (%)
Hartrampf 1987	Pedicled	432	0.5	5.2	5.2
Schusterman 1992	Pedicled	48	0	17	23
Elliott 1993	Pedicled	128	0	10	N/A
Kroll 1998	Pedicled	67	N/A	N/A	26.9
Paige 1998	Pedicled	127	N/A	10	12.6
Clugston 2000	Pedicled	252	0	2	7.1
Garvey 2006	Pedicled	94	8.5	58.5†	†
Schusterman 1994	Free	211	1	7†	†
Trabulsky 1994	Free	99	4	6	N/A
Kroll 1998	Free	49	N/A	N/A	8.2
Nieminen 1999	Free	185	1	4.3	N/A
Chang 2000b	Free	936	5.1 \$	6.2	N/A
Kroll 2000	Free	279	0	2.2	12.9
Nahabedian 2002b	Free	143	3.5	0	9.8
Scheer 2006	Free	46	4.3	6.5	9.0

N/A not reported. \$ 38,5 % of patients moderately or massively overweight. † includes partial cutaneous, and fat necrosis.

in the subcutaneous tissue. It develops later than cutaneous necrosis, generally one to six months postoperatively. The diagnosis is made clinically or with ultrasound or mammography. The fat necrosis area can be observed without surgical interventions, or resected, as needed (Kroll 2000). Partial flap loss is seen in 5–60 % of pedicled TRAM flaps and in 0–15 % of free TRAM flaps (Table IV).

Factors affecting the risk of partial flap loss in TRAM flaps include smoking and obesity. Cutaneous necrosis is seen more commonly in smokers than in non-smokers (Chang 2000a, Padubidri 2001, Selber 2006, Booi 2007). In addition, some studies suggest that smoking increases the incidence of fat necrosis (Kroll 2000, Selber 2006), while others report no effect. (Alderman 2002, Nahabedian 2002b). The role of overweight in development of cutaneous and fat necrosis of TRAM flaps is described in Section 2.7.2.

2.3. Blood flow in surgical flaps

2.3.1. Blood flow of the skin

The first accurate publication of blood flow to the skin was submitted by Harvey in 1628 (Harvey 1628). Tomsa subsequently described the subdermal and dermal plexuses of the skin in 1873 (Tomsa 1873), and Spateholz the direct and indirect perforators to the skin (Spateholz 1893). In 1889, Manchot described in detail

the cutaneous blood supply and identified distinct skin territories, each receiving its blood flow from its own source vessel (Manchot 1889). His work formed the basis of the studies of Salmon, who found that in reconstructive surgery a flap must include an arterial pedicle (Salmon 1936a, 1936b). Knowledge of blood flow of skin has since remained relatively unchanged.

Nowadays, the vasculature of the skin and subcutis is believed to consist of five vascular plexuses (Figure 4). The most superficial is the subepidermal plexus, beneath which run the dermal, subdermal, subcutaneous, and the fascial plexuses. Each plexus is a horizontal fine meshwork of interconnecting vessels. The plexuses have a huge capacity for distributing blood flow to the skin and subcutis. The dermal plexus with its muscular arteriolar vessels is the main thermoregulatory system, and the subdermal plexus with its thin-walled capillaries is the main site for nutrient exchange (Blondeel 2006).

The blood flow to the vascular plexuses of the skin and subcutis is supplied through the perforator arteries, which arise from source arteries below the deep fascia (Blondeel 2006). They are described in Section 2.3.3.

2.3.2. Regulation of cutaneous blood flow

Normal blood flow to the skin is about 20 ml per 100 g of tissue at rest. The blood flow to

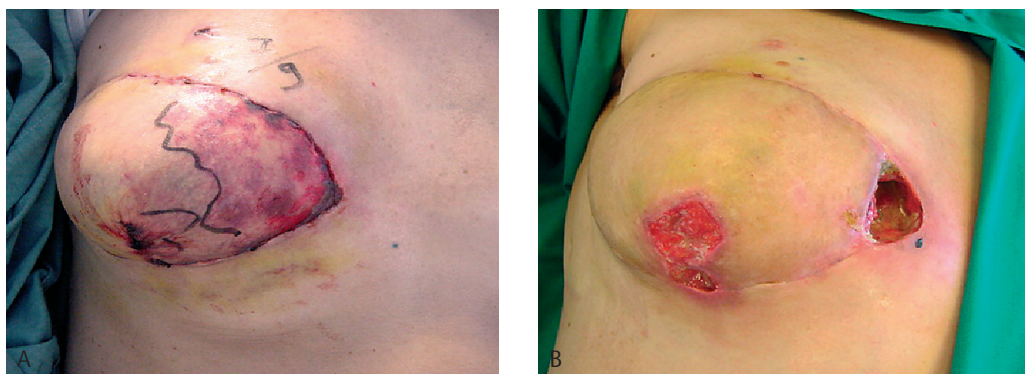


Figure 3. The right breast of a patient who underwent breast reconstruction with a pedicled TRAM flap. Cutaneous necrosis on the first (A) and seventh (B) postoperative day. The necrosis is seen at the edge of the contralateral skin of the flap (zone IV), now situated on the medial side of the new breast. Surgical revision was required.

tissues of the body is controlled by the needs of the tissue itself (Guyton 2001). Several factors regulate the vascular tone of skin vessels, including the autonomic nervous system, cerebral functions such as emotions, ocular stimuli, and sounds, and other factors such as orthostatic position, nutrients, medicines, and smoking. Peripheral vessels are in constant vasomotion, reflected as rhythmic contractions six to eight times per a minute (Vedder 2005).

Cutaneous blood flow is regulated at the local and systemic level and by the baroreceptor mechanism. In the local control of cutaneous blood flow, the microvessels of the skin continuously monitor the levels of oxygen, nutrients and carbon dioxide. They regulate the circulation by constricting or dilating local blood vessels within seconds to minutes to provide the ideal level of tissue blood flow needed for each type of activity. Hypercapnia, hypoxia, and acidosis cause vasodilation. Increased tissue perfusion can induce a myogenic reflex seen as vasoconstriction and decreased blood flow. Blood flow of skin decreases also as a result of elevated viscosity of the blood and local hypothermia (Guyton 2001, Vedder 2005),

Systemic regulation can occur neurally and humorally. The sympathetic vasoconstrictor and vasodilator nerves modify the vessel tonus. The cutaneous arteriovenous anastomoses are richly innervated by the sympathetic vasoconstrictor nerves (Lossius 1993, Crandall 1996).

A neural stimulus through the sympathetic fibers to the α -adrenergic receptors of the vascular smooth muscle induces constriction of the precapillary sphincters and arterioles, and the blood flow is directed, instead of to the capillaries, through arteriovenous shunts to venules and veins. Accordingly, sympathetic stimulation of the β -adrenergic receptors induces vasodilation. The sympathetic regulation through serotonergic receptors situated at arteriovenous anastomoses induces vasoconstriction. Humoral regulation means regulation of blood flow by hormones, ions, and other substances of the body fluids, stimulating the specific receptors in the tissue. These substances can approach the tissue through the bloodstream or be secreted locally in the tissue. Norepinephrine, epinephrine, angiotensin, vasopressin, serotonin, thromboxane A₂, and endothelin are the most important vasoconstrictors. Bradykinin, prostacyclin, and histamine are examples of vasodilatory substances (Guyton 2001, Vedder 2005).

2.3.3. Principles of blood flow in flaps

In reconstructive surgery, even large tissue defects can be successfully repaired with flaps. Planning and choosing of the most suitable flap for each purpose is based on knowledge of blood flow and behavior of the flap. The flaps

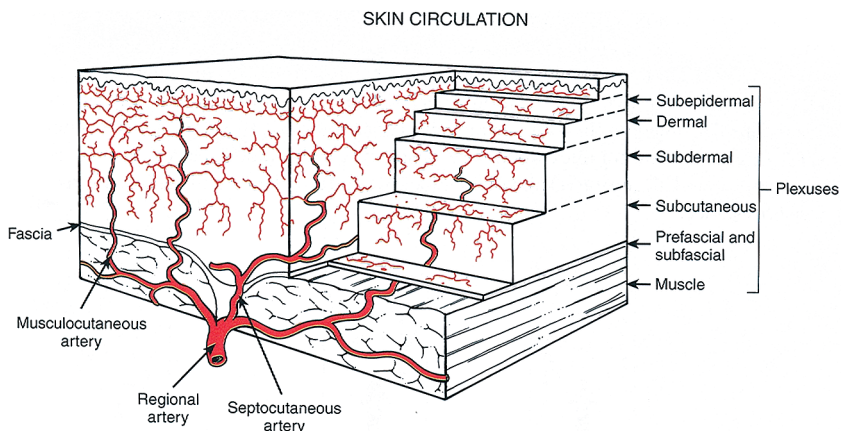


Figure 4. A schematic representation of the vascular structure of the skin and subcutis. From Mathes SJ and Nahai F: *Reconstructive Surgery; Principles, Anatomy & Technique*. Churchill Livingstone Inc. (Elsevier), New York, USA 1997, p 15. Printed with the kind permission of the publisher.

can be classified, based on their structure, as muscle or fascial flaps. If skin is included in the flap, it is called analogously a musculocutaneous or fasciocutaneous flap. Other tissues with vascular connections to the muscle or fascia can also be included in the flap, e. g. bone, tendon, bowel, or omentum. The known flaps have a fairly constant pattern of blood flow through a vascular pedicle consisting of an artery and vein. The pedicle or pedicles are called dominant if they can provide the blood flow of the whole flap area. Minor pedicles cannot guarantee the flap blood flow alone, without the dominant pedicle (Mathes 1997, Blondeel 2006).

The angiosome concept developed by Taylor and Palmer (Taylor 1987) lies at the foundation of harvesting flaps in modern reconstructive surgery. The angiosome was described as a three-dimensional composite unit of tissue supplied by a specific source artery. The composite contains muscle, nerve, connective tissue, bone, and overlying skin. The body is divided in 40 angiosomes based on named source arteries, and some angiosomes are divided into smaller territories. The angiosomes are usually interconnected with adjacent angiosomes through reduced caliber choke anastomotic vessels or sometimes through ordinary anastomoses without caliber reduction. The outer limit of each territory is defined by the position of choke vessels. The choke vessels can regulate the blood flow of the angiosome by dilating or constricting as needed.

The venous drainage of the body mirrors the arterial supply in the deep tissues and in most areas of the skin and subcutis in the head, neck, and torso. The choke arteries are accompanied by oscillating veins (Taylor 1990). Each angiosome consists of matching arteriosomes and venosomes.

The elevation of a flap is followed by loss of sympathetic innervation and spontaneous release of vasoconstricting neurotransmitters. Many nutrient vessels are also cut. These mechanisms lead to an acute decrease in flap flow (Vedder 2005).

In experimental studies, after denervation blood flow has been observed to increase in skeletal muscle (Chen 1991, Chen 1992, Siemi-

onow 1994, Wang 1995) and in skin flaps (Finseth 1978, McKee 1982) because of arteriolar vasodilation and increased capillary perfusion. The effect of sympathectomy on muscle blood flow has been investigated in rats. Proximal sympathectomy with somatic denervation caused a triphasic dynamic response in the peripheral microcirculation. During the first few hours there is an initial hyperadrenergic phase seen as vasoconstriction. After 24 hours, a nonadrenergic phase with vasodilation can be seen. This can last up to two weeks, after which a sensitized phase starts, with hyperresponsiveness of the microvessels to vasoactive substances and a further increase in microcirculation (Banbury 1999).

In animal studies, within a few hours after flap elevation blood flow in the tip of the flap decreases markedly, while blood flow in the proximal flap is preserved. The blood flow gradually increases to normal levels over the next month (Vedder 2005).

Neovascularization from the surroundings of the flap also increases the flap blood flow. Within minutes of closing a small blood vessel, the nearby collaterals are dilated as a neurogenic or humoral phenomenon. During the next hours further opening of collaterals occur; the process continues for many months after the operation. Hypoxia is thought to stimulate formation of local growth factors, such as VEGF, fibroblast growth factor, and angiogenin, which in turn stimulate new vessel growth from the small vasculature (Guyton 2001).

Clinical studies have found that the weight-related intake of blood flow depends on the type of the free flap. Flaps with a large portion of fat, like the TRAM flap, have a low intake of blood compared with flaps containing abundant muscle (Lorenzetti 2001a). In free flaps, the flap blood flow is believed to be dependent on the hemodynamic requirements of the flap and not on the characteristics of the recipient artery (Lorenzetti 2001b).

Pedicles of muscle and fascia

The blood flow of muscles is based on one or more vascular pedicles entering the muscle between its origin and insertion. The muscle pedicle consists of an artery and paired ac-

companying veins, which are branches of the specific regional artery and vein.

The vascular supply of muscles has been classified to five types according to the pattern of blood flow by Mathes and Nahai (Mathes 1981). The principles of classification of the vascular supply of muscles and fascia are shown in Figure 5.

According to the classification of Mathes and Nahai:

- type I muscles are supplied by a single vascular pedicle (e. g. the tensor fascia lata muscle),
- type II muscles have one dominant pedicle and one or more minor pedicles (e. g. the gracilis muscle),
- type III muscles have two large vascular pedicles arising from separate regional vessels or the pedicles are located on opposite sides of the muscle (e. g. the rectus abdominis muscle),
- type IV muscles have many segmental

pedicles (for example the sartorius muscle)

- and type V muscles receive their blood flow through one dominant vascular pedicle and several secondary pedicles (e. g. the latissimus dorsi muscle).

The blood flow of deep fascia is based on vascular pedicles entering the deep surface of the fascia and forming the vascular meshworks of the subcutis and skin (see Section 2.3.1). The vascular pedicles from deep fascia to the skin represent one of three types (Figure 5):

- Type A is a direct cutaneous pedicle. It originates from the regional vessels, runs closely beneath and superficially to the deep fascia and gives off branches to many perforators to the skin. The SIEA flap used for breast reconstruction is based on a type A fasciocutaneous pedicle.
- Type B is a septocutaneous (or intermuscular) pedicle running from major vessels between muscles up to the skin. In the extremities, most perforators are of the sep-

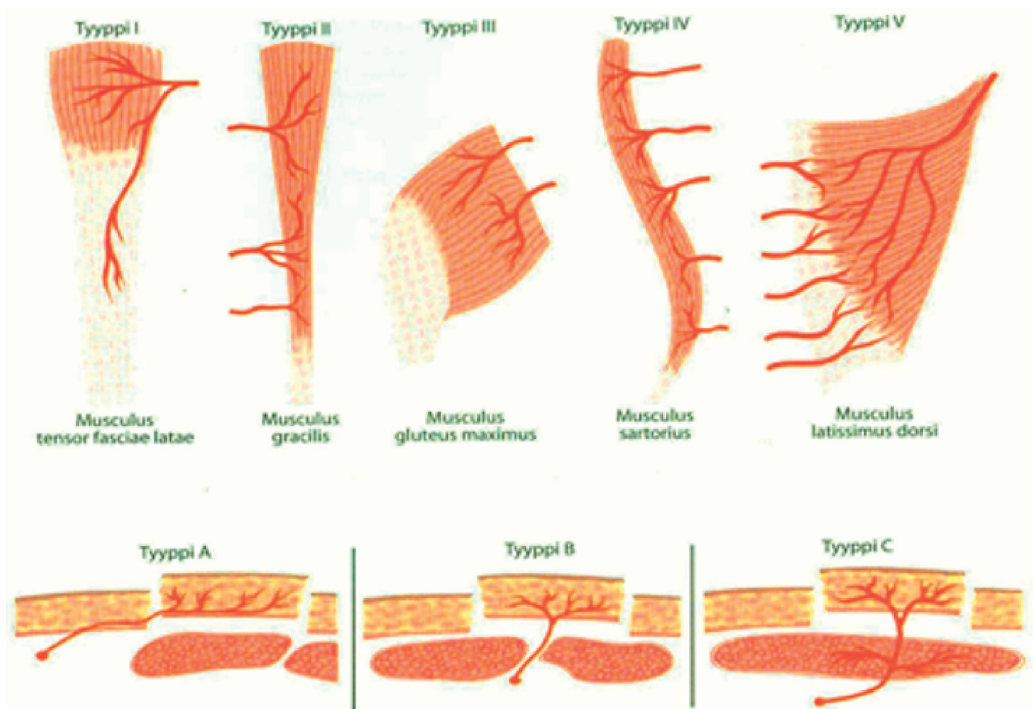


Figure 5. The principles of classification of the vascular supply of muscles and fascia based on Mathes and Nahai (1981). From the article Tukiainen E, Suominen S: Kudoskielekkeet rekonstruktivisen plastiikkakirurgian arkea. Duodecim 2007; 123: 987-997, with kind permission of Suomalainen Lääkäriseura Duodecim. The rectus abdominis muscle of the TRAM flap represents type III muscle and its pedicle represents a fasciocutaneous pedicle (type C).

tocutaneous type. For example, the radial forearm flap has a type B pedicle.

- Type C is a musculocutaneous pedicle. It runs from the regional vessels through muscle, and then travels as a perforator through the overlying deep fascia, finally participating in the subcutaneous and skin vascular networks. In the human body, musculocutaneous pedicles dominate on the trunk area, seen as perforators passing through flat large muscles. The anterior thigh flap and the cutaneous part of the TRAM flap have musculocutaneous pedicles (Mathes 1997, Blondeel 2006).

2.3.4 Blood flow in the TRAM flap

The conventional TRAM flap is an asymmetric flap consisting of part of one of the rectus abdominis muscles, and a transverse elliptiform area of fascia, subcutis, and skin above the muscle.

The rectus abdominis muscle is a type III muscle with two main vascular pedicles (see Section 2.3.3). The two main pedicles are the superior epigastric vessels and the deep inferior epigastric vessels. The superior epigastric artery (SEA) usually arises from the internal mammary artery and enters the rectus abdominis muscle on its dorsal surface at the costal margin, then running in the inferior direction. In about 10 % of patients, the SEA arises from the costomarginal artery (Milloy 1960, Arnold 1972, Miller 1988). The deep inferior epigastric artery (DIEA) arises from the external iliac artery and enters the rectus muscle on its undersurface below the arcuate line. The SEA and DIEA pedicles run inside the muscle as single-, double-, or triple-branched arteries to the periumbilical region (Boyd 1984, Taylor 1984, Moon 1988, Watterson 1988), where the DIEA and SEA angiosomes communicate with each other through the choke vessels (see Section 2.3.3). Anatomical and radiographic studies have shown that the DIEA is more significant than the SEA in supplying the skin of the anterior abdominal wall (Boyd 1984).

The so-called choke vessels are of macroscopic caliber in about 40 % of people; in the

rest, they are microscopic. In addition to the periumbilical choke vessels, the DIEA is connected through choke vessels also inferiorly with the SIEA, inferolaterally with the superficial circumflex iliac artery, and superolaterally with the lateral cutaneous branches of the six lowest intercostal segmental arteries (Taylor 1987, Miller 1988). Recently, communications between the costomarginal, musculophrenic, and intercostal arteries have been found (Marin-Gutzke 2005). The effect of the caliber of choke vessels on their function has not been studied.

Blood flow to the skin and subcutis of the lower abdominal and periumbilical areas is supplied through the musculocutaneous perforators. These perforators run as branches from DIEA and SEA systems into and through the rectus muscle to the vascular plexuses of the overlying fascia and skin. The perforators run in two parallel rows through the anterior rectus sheath on both sides of the linea alba, the medial row 1–2 cm laterally to the linea alba, and the lateral row 2–3 cm medially from the lateral edge of the rectus muscle. The highest concentration of major perforators is in the paraumbilical area. Their caliber varies from very narrow to several millimeters (Boyd 1984, Moon 1988). The perforators from DIEA and SEA have been investigated later. In two cadaver studies, the anatomy of DIEA perforators showed a homogenic pattern between individuals (Nakajima 1998, El-Mrakby 2002), while in two cadaver and ex vivo flap studies the perforators of DIEA varied markedly in their orientation and size (Ohjimi 2002, Tregaskiss 2007). The perforators of SEA were found to have a more consistent course (Tregaskiss 2007). The branching pattern of the DIEA has been examined recently with computed tomography angiography. DIEA was observed to be single, bifurcating, or trifurcating. The trifurcating type had the largest amount of perforators through the rectus muscle (Rozen 2008).

In the pedicled TRAM flap, blood flow is supplied through the SEA, which is the non-dominant pedicle of the anterior abdominal skin and subcutis (Boyd 1984). The free TRAM flap receives its blood supply through its domi-

nant pedicle DIEA, which is anastomosed to the recipient artery in the thoracic area.

In pedicled TRAM flaps, blood flow to the ipsilateral skin and subcutis island, situated over the rectus muscle, comes through paraumbilical and infraumbilical perforators, filling in a retrograde fashion from the superior epigastric system by means of the choke vessels. (Boyd 1984). The contralateral skin and subcutis island receives its blood supply through anastomotic channels crossing the midline in the subdermal plexus (Taylor 1984) and by distinct subcutaneous arteries, mostly situated near the umbilical area (Kaufman 1985). The contralateral part of the skin-subcutis island is in fact a random-type flap.

In free TRAM flaps, blood flow to the ipsilateral skin and subcutis comes mainly from the DIEA through the perforators. The contralateral island of the free TRAM flap is supplied in the same way as in the pedicled flap.

The venous drainage of the TRAM flap skin is through paraumbilical perforator veins, in a similar way as the arterial flow, to the deep inferior and the deep superior epigastric veins. Midline crossover runs through several branches of the superficial and deep epigastric veins. In the deep inferior epigastric pedicle, two large venae comitantes drain to the iliac circulation. These veins are larger than the ones following the SEA (Schefflan 1983b, Watterson 1988). In addition, the superficial inferior epigastric veins add to the abundant venous outflow of the inferior veins. The deep inferior epigastric veins have valves that prevent retrograde flow (Costa 1987, Taylor 1990). The periumbilical choke vessels have a bi-directional venous flow. When the pedicled TRAM flap is raised, distal venous outflow has to reverse from the inferior direction to the superior epigastric veins, passing the venous valves through the choke vessels (Taylor 1987, Moon 1988).

To understand the different types of circulation and to predict survival in different parts of the TRAM flap skin, the skin of the flap island has been divided into four zones based on clinical experience and quality of perfusion (Hartrampf 1982, Schefflan 1983a and 1983b). The zones are presented in Figure 6. The skin directly overlying the ipsilateral rectus muscle

is considered zone I, and the same area on the contralateral side zone II. The skin lateral to the ipsilateral muscle is called zone III, and the skin lateral to the contralateral muscle zone IV.

The zones were initially numbered in the order of assumed degree of perfusion. Cutaneous blood flow has been thought to be most reliable in zone I, and fairly reliable in the medial parts of zone III as well as in the medial parts of zone II. The distal end of zone III and the lateral part of zone II are less reliable. Zone IV should be discarded routinely because it is prone to necrosis. When elevating a flap, the blood flow in an adjacent angiosome has been speculated to be quite reliable, becoming less reliable in more distant angiosomes, especially across the midline, as in zone IV in a TRAM flap (Taylor 1987). It has been suggested that zones II and III should be in reverse order because according to anatomical studies the ipsilateral perfusion is always better than the undirect perfusion to contralateral skin areas (Dinner 1983, Moon 1988).

Hemodynamic studies on blood flow in TRAM flaps have not been published before the studies presented in this thesis. The studies published thereafter are presented in the Discussion.

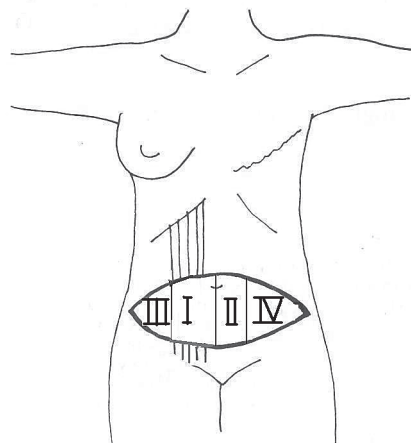


Figure 6. The four zones of the TRAM flap based on cutaneous blood flow.

2.3.5. Temperature and the cutaneous blood flow

Human body temperature is controlled centrally by the thermoregulatory center in the preoptic/anterior hypothalamus in the brain. It receives information from the core and surface temperatures and coordinates the efferent responses regulating the temperature. During heat stress, an increase in core or surface temperature leads to loss of heat via sweating and cutaneous vasodilation. During cold stress, reduced temperatures cause reflex decreases in heat dissipation by cutaneous vasoconstriction and simultaneously heat production by shivering. During normothermia, skin blood flow averages about 5 % of cardiac output. The cutaneous blood flow varies depending on body temperature; during maximal vasoconstriction, as in cold stress, the absolute amount of blood in the skin is near to zero, and during maximal vasodilation in heat stress the cutaneous blood flow can consist of up to 60 % of cardiac output (Rowell 1974, Boulant 2000, Kellogg 2006).

The degree of thermoregulatory vasoconstriction can be evaluated by the skin temperature gradient (T_{grad}), which is determined as the difference between finger and arm temperatures (Stoen 1990). T_{grad} correlates with fingertip blood flow in humans (Rubinstein 1990, Akata 2004) and is thought to indicate the state of the arteriovenous shunts (Rubinstein 1990). T_{grad} exceeding 4 °C is generally accepted to indicate marked vasoconstriction, and T_{grad} less than 0 °C is considered a sign of vasodilation (Stoen 1990). The concept thermoregulatory threshold is used for the level of core temperature at the stage when thermoregulatory vasoconstriction begins (Stoen 1990, Belani 1993, Kasai 2003, Pezawas 2004).

2.3.6. Effect of general anesthesia on thermoregulation and cutaneous blood flow

Unanesthetized subjects do not become hypothermic in the ambient temperature of an operating room because thermoregulatory vasoconstriction with shivering usually maintains

the core temperature near 37 °C (Stoen 1990, Sessler 1997). During general anesthesia core temperature decreases in three phases (Sessler 1991, Hynson 1992, Matsukawa 1995a). During the first hour the core temperature decreases at least 1 °C because of the core-to-peripheral redistribution of body heat, caused by anesthesia-induced inhibition of tonic vasoconstriction. After this, the core temperature decreases slowly, in a linear fashion when heat loss exceeds metabolic heat production because of cooling. Finally, the core temperature stabilizes when thermoregulatory vasoconstriction develops, reducing cutaneous heat loss and keeping metabolic heat in the core. General anesthesia reduces the thresholds for vasoconstriction and shivering by approximately 3 °C (Sessler 1997) if the development of hypothermia is not prevented. In reconstructive plastic surgery, the operations usually continue for many hours, and thermoregulatory vasoconstriction, lasting for several hours postoperatively, frequently develops. The amount of uncovered skin during the operation also contributes to development of hypothermia. During breast reconstruction with a TRAM flap large areas of the patient's skin are exposed, because there are two surgical teams working simultaneously, one on the abdomen and the other on the chest.

All inhaled anesthetics induce vasodilation in the skin by inhibiting central thermoregulatory control (Ozaki 1995, Ozaki 1997). Isoflurane has a more potent vasodilatory effect on skin blood flow than halothane (Mulholland 1994). The thermoregulatory threshold is highest for nitrous oxide and halothane, and lowest for sevoflurane and isoflurane; an inverse correlation with the anesthetic dose has been found (Smith 1990, Stoen 1990). Also intravenous propofol inhibits the central thermoregulatory control, thus leading to redistribution hypothermia (Leslie 1994, Matsukawa 1995b). In addition, propofol produces a profound, peripheral arterial and venous dilation (Bently 1989), causing an increase in skin blood flow. The agent used for induction of anesthesia affects the degree of hypothermia developing during the operation. The hypothermia is more profound

with intravenous propofol than with sevoflurane inhalation as an induction agent (Ikeda 1999). Patients developing even a short-lasting propofol-induced vasodilation during the induction of anesthesia have developed a marked hypothermia compared with patients receiving inhalational induction with sevoflurane (Ikeda 1999). Ketamine as an induction agent causes considerably less hypothermia than propofol (Ikeda 2001), as it is an arterial vasoconstrictor. Intraoperative thresholds for thermoregulatory vasoconstriction depend on the size, shape, and age of the patient, depth of anesthesia, degree of pain stimulus, and the method of temperature management. (Sessler 1988, Sessler 1992, Washington 1992, Kurz 1993, Xiong 1996.)

In humans anesthesia mainly affects cutaneous blood flow, while subcutaneous blood flow remains virtually unchanged (Saumet 1988).

2.4. Monitoring of blood flow in flaps

2.4.1. Methods used to measure blood flow in surgical flaps

Monitoring of blood flow in surgical flaps is essential to detect any disturbances in flap viability. If signs of compromised blood flow are observed, urgent measures are taken to reperfuse the flap. An ideal monitor of flap perfusion is simple, reliable, reproducible, and sensitive and should give information about perfusion of the whole flap. A selection of methods has been developed for monitoring blood flow in flaps. However, only a few methods are suitable for continuous clinical use in superficial and buried flaps. The methods most widely used are presented in the next sections.

The simplest method to monitor the flap is *clinical observation* of flap color and capillary refill after gentle manual pressure. A pale color without capillary refill can indicate arterial insufficiency and a blueish color with a very fast refill can be a sign of venous congestion. Sticking the flap with a needle and observing the color of blood oozing from the pinprick holes can also be used as a simple monitor (Dagum 1995).

Temperature of the flap is an old method for monitoring flap blood flow in replanted body parts and flaps. It is considered reliable in ideal circumstances (Sloan 1985, Kaufman 1987) and is still a popular method for monitoring replanted digits. However, ambient temperature, core temperature, humidity, light, and vasomotor responses can affect surface temperature, which has been found to react slowly when blood flow decreases. In buried flaps, measuring the temperature differences between thermocouple probes placed proximally and distally to the anastomosis is considered more reliable than observing the surface temperature (May 1983).

Several chemical techniques have been applied for monitoring of flaps. Tissue perfusion can be estimated after an intravenous injection of *fluorescein* (Lange 1942, McCraw 1977, Graham 1983). Adequately perfused tissue fluoresces under ultraviolet light. The method is useful at the time of elevation of a skin-containing flap, but it is suitable only for a single measurement in 24 hours, and is thought to underestimate the amount of surviving tissue. Continuous measurements can be performed with a fiber-optic dermofluorometer, which has been successfully used in monitoring perfusion of pedicled and free flaps (Silverman 1980, Casanova 1988, Whitney 1992). *Indocyanine green* is also a fluorescent dye with less side-effects than fluorescein. It has given promising results in monitoring blood flow in flaps (Eren 1995). *Radioactive isotopes*, including technetium-99m with a half-life of 6,01 hours, (Aygit 1999), xenon-133 with a half-life of 5,27 days (Tsuchida 1990), and sodium-22 with a half-life of 2,6 years (Harrison 1981), have been given to patients and the perfusion has been monitored with scintigraphy. They can be used for monitoring perfusion in free and pedicled superficial and buried flaps, but they are not suitable for continuous monitoring. *Hydrogen gas clearance* gives repeated and quantitative measurements of tissue blood flow in buried and superficial flaps (Aukland 1964, Glogovac 1982).

Flap blood flow has been assessed with methods based on the tissue metabolism. Subcutaneous and intramuscular *pH* measured

with implantable probes have decreased in flaps with impaired blood flow as a consequence of increased anaerobic metabolism (Raskin 1983a). *Microdialysis* is a technique analyzing the metabolic activity of tissue by means of microdialysis catheters implanted in the tissue. Glucose, glycerol, lactate, and pyruvate concentrations can be measured from the dialysate. The method was initially used in brain monitoring, but it has been successfully applied in flap monitoring as well (Bito 1966, Ungerstedt 1997, Edsander-Nord 2002, Setälä 2006, Setälä 2007). In ischemic free flaps, decreased glucose concentrations and increased lactate levels and lactate/pyruvate ratios have been observed (Udesen 2000, Setälä 2006).

Near-infrared spectroscopy (NIRS) is a noninvasive continuous method of monitoring blood flow of tissue. It was introduced ten years ago to monitor circulation in surgical flaps (Hayden 1996, Thorniley 1998). It measures the hemoglobin and oxyhemoglobin concentrations in tissue up to 10 cm in depth. The hemoglobin concentrations reflect changes in blood volume, thus indirectly indicating the amount of perfusion. NIRS has been able to differentiate between arterial, venous, and total vascular occlusion in flaps (Irwin 1995, Thorniley 1998). It is considered a promising tool for measuring perfusion in flaps (Scheufler 2004). *Photoplethysmography* estimates the fluid volume of tissue by detecting differences in light absorption of the skin. Light emitted by a cutaneous diode probe is reflected by hemoglobin in the erythrocytes of dermal capillaries of the skin. The reflected light is received by a photo detector and analyzed as light intensity along a frequency spectrum, with the noise removed. The method can differentiate between perfused and nonperfused tissue and provides a good estimate of pedicle vessel patency (Stack 1998). Newer modifications have been developed using a green-light emitting diode, giving an accurate estimate of possible flap ischemia (Futran 2000).

The Doppler effect has been widely used for measuring the velocity of blood flow since the 1960s (Strandness 1966). The main modifications are the *Doppler ultrasonography* and the *laser Doppler flowmetry* (LDF). The LDF

is explained in detail in the next sections. In conventional Doppler ultrasonography, the probe emits ultrasounds to a tissue up to several centimeters in depth, and the sound waves reflected from blood cells in large arteries and veins are analyzed. The blood flow in arteries and veins has a typical signal, being triphasic in arteries and lower pitched and continuous in veins. When blood flow in a vessel decreases, the signal changes. When monitoring flap pedicles, the adjacent large vessels from other tissues may disturb the accuracy of the ultrasound Doppler signal. Miniature implantable Doppler probes attached to a thin cuff fitting around an effluent vein or distally to the arterial anastomosis have been developed to overcome this problem (Swartz 1988, Swartz 1994, Kind 1998).

The measurement of local partial pressure of oxygen is a popular way to observe blood flow in flaps. It can be measured on the surface of the flap with a *transcutaneous oxygen tension* monitor ($P_{tc}O_2$) or inside the tissue with an implantable *tissue oxygen tension* probe. $P_{tc}O_2$ is explained in detail later in the text. Tissue oxygen tension monitoring has been developed since 1960s (Hunt 1964, Chang 1983), gradually becoming a popular monitor of local brain blood flow in neurosurgery and neurocritical care (Dings 1998). It is considered a reliable method for continuous monitoring of blood flow in superficial and buried flaps as well (Mahoney 1988, Hirigoyen 1997).

Laser Doppler flowmetry

The laser Doppler flowmeter is a continuous monitor of microcirculation. It was introduced about 30 years ago following the development of laser technologies and fiber-optic systems (Stern 1975, Holloway 1977, Nilsson 1980a, Nilsson 1980b). This method of measuring cutaneous blood flow is based on the frequency shift of the laser light. A monochromatic He-Ne laser beam is emitted through an optical fiber on the skin surface where it permeates the skin to a depth of 0,5–1 mm. The thickness of the epidermis, the most superficial layer of skin, is 0,05–0,2 mm and the thickness of the dermis below is 0,3–3 mm. The LDF beam is assumed to reach the dermis, and, in some cas-

es, the subcutaneous layer under the dermis. When the laser beam hits moving blood cells in the blood vessels, the frequency of reflecting laser light is spectrally broadened, while the frequency of light reflected from static tissues does not change. A photodetector in the LDF probe receives the backscattered light beams, which are processed by the instrument, and the result is produced as a low-noise input signal linearly related to the number and velocity of moving blood cells in the measured field at low or moderate flow rates (Nilsson 1980b, Tenland 1982, Bengtsson 1983, Svensson 1983). The LDF output signal is presented in arbitrary perfusion units, which is a relative value. The signal can be expressed as a continuous oscillating line in a pen-recorder.

Initially, LDF could only be used for monitoring the skin, including the capillary loops of the dermal plexus, with a skin probe, but today a variety of different probes are available, including implantable miniprobes for monitoring different tissues, e.g. the muscle of buried flaps, and probes with different fiber separations suitable for monitoring vascular beds at different depths.

The traditional LDF measures the blood flow at a single point, and repeated measurements give the trend in the perfusion at this determined site. Recently, a new development of LDF has been made, enabling blood flow in a larger area to be measured continuously. The laser Doppler perfusion imaging (LDPI) is a noncontact two-dimensional system, where the laser beam scans a horizontal area with the help of mirrors integrated in the probe system, and processes an image containing at least 100 measurement sites. LDPI gives quantitative information on a specific region of interest (Essex 1991, Wårdell 1993) and has proven to be a useful and reliable monitor of perfusion in dermatology, plastic surgery, diabetology, and wound healing (Arnold 1995, Fullerton 2002).

LDF is generally considered a good indicator of changes in blood flow in clinical plastic surgery (Heden 1985, Svensson 1985a, Svensson 1985b, Yuen 2000, Heller 2001), although some authors have been sceptical (Walkinshaw 1987, Banic 1990, Hickerson 1990). It is ac-

cepted that the variable to be monitored is the trend in perfusion and not the absolute value given by the monitor. It has been suggested that if the relative flow of a flap falls to 50 % of its initial flow for more than 30 minutes, the flap should be aggressively observed, and in cases with very low LDF readings the flap should be immediately explored (Heller 2001). LDF is used for postoperative flap monitoring in many centers.

The LDF value is influenced only minimally by wide differences in oxygen tensions. The LDF level varies greatly between different individuals and also between different measuring sites in one person (Tenland 1982), but the cutaneous LDF values for the same donor tissues have been similar between several volunteers (Goldberg 1990). Daily LDF variations of 20–30 % occur frequently. A LDF value measured continuously or repeatedly at exactly the same site in a person is considered reliable (Tenland 1982). The reliability of the LDF signal is affected by improper attachment or movement of the probe, location of the probe over a larger vessel, or technical problems in the apparatus or the laser beam (Heden 1985, Clinton 1991, Svensson 1993).

Transcutaneous oxygen tension

$P_{tc}O_2$ is among the oldest methods for flap monitoring (Achauer 1980, Harrison 1981, Serafin 1981, Svedman 1982, Smith 1983). $P_{tc}O_2$ is an indirect indicator of blood flow, reflecting oxygen delivery and consumption in the skin (Achauer 1984). The method measures the oxygen tension of skin through a permeable membrane. The probe heats the skin to a temperature of about 43.5 °C to induce maximal vasodilation to minimize the arterial-to-skin surface oxygen gradient.

The probe requires calibration against an oxygen-free zero solution and ambient pressure before each measurement and a stabilization period of 10–20 minutes after each replacement. $P_{tc}O_2$ is a little lower than arterial oxygen tension (PaO_2) in normal subjects (Brown 1984).

2.5. Endothelin

2.5.1. *Endothelin and vasoconstriction*

Endothelin-1 (ET-1), described in 1988, is one of the most potent vasoconstrictors (Yanagisawa 1988). It is a 21-amino acid polypeptide mainly synthesized and secreted by vascular endothelial cells (Yanagisawa 1988, Remuzzi 1993). Stimuli inducing the production of endothelin include cold, thrombin, increased transmural pressure, stretch, hypoxia, and decreased shear stress on the vascular lining (Yanagisawa 1988, Yoshizumi 1989, Gandhi 1994). The vasoconstrictory effect of ET-1 appears to be mediated via the ET-A receptors situated in smooth muscle cells, while the ET-B receptors are situated in vascular smooth muscle cells and endothelial cells; they also mediate the vasodilatory effects of ET-1, depending on the balance between vasoconstriction and vasodilation (Seo 1994, Mickley 1997). The binding of ET-1 to smooth muscle cells causes a prolonged vasoconstriction (Remuzzi 1993), which is intense in arteries and even stronger in veins (Cocks 1989). ET-1-induced vasoconstriction results in an increase of blood pressure, but ET-1 does not affect heart rate (Remuzzi 1993, Gandhi 1994). It is involved in the control of cardiovascular function by maintenance of vascular tone in man (Remuzzi 1993, Haynes 1994).

ET-1 is a local hormone and more than 80 % of its secretion from the endothelium is towards the underlying muscle and not towards the vessel lumen. Plasma ET-1 concentration is thought to increase only when very high amounts of ET-1 are released from the tissues (Remuzzi 1993, Gandhi 1994). Plasma ET-1 concentrations of 0.5–5 pg/ml have been detected in healthy humans (Karwatowska-Prokopczuk 1990). Elevated ET-1 levels have been observed during surgery (Hirata 1989) and after major operations (Shirakami 1995).

2.5.2. *Effect of different substances on endothelin levels*

In experimental and clinical studies, plasma endothelin release and subsequent vasocon-

striction have been suppressed by calcium antagonists (Kiowski 1991, Liu 1994, Kobayashi 2001, Yakubu 2002). The dihydropyridine calcium channel antagonist nicardipine, and the angiotensin-converting enzyme (ACE) inhibitor enalapril suppress plasma-ET-1 levels in hypertensive patients with type 2 diabetes (Iwase 2000). Felodipine is a dihydropyridine calcium antagonist with a powerful vasodilatory capacity. It reduces peripheral resistance by relaxing arterial resistance vessels without causing negative inotropic effects (Ljung 1985). Before the studies of this thesis, no reports of its effects on ET-1 levels had been published.

ET-1 production has also been suppressed by statins, which inhibit ET-1 production at the level of gene transcription (Hernández-Perera 2000), by ET-A-receptor antagonists (Liu 1994), and by nonselective ET-A/ET-B antagonists such as bosentan (Kiowski 1995, Sutsch 1998).

2.5.3. *Endothelin and surgical flaps*

Studies on surgical flaps indicate that endothelin may be an important regulator of the microcirculation and affect the development of tissue necrosis. In dogs, intra-arterial infusion of ET-1 reduced blood flow in skin flaps (Samuelson 1992). Intraperitoneal injection of ET-1 has decreased the length of skin flap survival in rats (Tane 1995).

The relation of ET-1 levels and ischemia has been investigated in experimental flaps. Elevated plasma ET-1 levels have been measured in ischemic island epigastric flaps (Matsuzaki 1993, Hjortdal 1994, Pang 1995,) and increased levels of ET-1 have been found on vascular walls of the pedicles of isolated free flaps submitted to prolonged ischemia (Pang 1998). Progressive venous stasis has induced greater production of ET-1 than arterial ischemia (Menger 1992).

ET-1 concentration of the blood flowing from the pedicle vein of free TRAM or DIEP flaps has been evaluated in 20 women. ET-1 concentration increased during the operation in flaps, but not in peripheral blood (Lantieri

2003). The concentration of ET-1 in different parts of experimental random pattern skin flaps has been investigated. In the early post-operative hours, the highest levels of ET-1 have been measured in the proximal flap (Tane 1995, Inoue 1998). ET-1 is speculated to restrict blood flow by inducing vasospasm on the proximal parts of the flap (Inoue 1998). In one study, endogenous ET-1 level was highest in the proximal flap for the first 24 hours, thereafter gradually decreasing, and increased in the first week in the distal flap. The distal ET-1 level correlated with the incidence of necrosis (Mobley 2003).

In experimental flaps, administration of an ET-A receptor antagonist FR-139317 (Tane 1995, Inoue 1998) and a combined ET-AB receptor antagonist tezosentan (Erni 2005) has improved postoperative flap blood flow and flap survival. A recent study shows, however, that the increasing effect of ET-A antagonist BQ-123 or ET-AB antagonist PD-142893 on flap blood flow is not seen until 5–7 days after flap elevation (Wettstein 2007). In the same experimental study, administration of an ET-B antagonist BQ-788 increased tissue survival significantly. An increase in flap blood flow was observed on the first day after flap elevation (Wettstein 2007).

2.6. Effect of different interventions on blood flow in the flap

Several interventions have been attempted to prevent ischemia and improve blood flow in flaps, especially in high-risk patients. The delay procedure means restricting of flap blood flow before the planned reconstruction to produce, in the distal portions of the flap, moderate ischemia, which does not cause necrosis. This method is a type of ischemic preconditioning. The delay procedure is performed one to four weeks before the final operation date by elevating part of the flap, but leaving the pedicle uncut or by ligating one of the pedicles in flaps with more than one dominant pedicle. Selective embolization of one of the pedicles has also been successfully used as a delay procedure in pedicled TRAM flaps (Scheufler 2000). A

delay procedure in TRAM flaps was suggested by Hartfampf in his initial publication (Hartfampf 1982). Surgical delay of a flap has been shown to lead to dilation of the choke vessels between adjacent territories. It is a permanent and irreversible event, with a maximal effect between 48 and 72 hours after raising the flap (Dhar 1999). Incidence of necrosis was significantly lower in pedicled TRAM flaps with ligation of the superficial and deep inferior epigastric arteries one month before the reconstruction than in flaps without the delay procedure (Ribuffo 1997).

To find a pharmacologic agent capable of preventing or reducing flap ischemia, many substances have been investigated. A variety of sympatholytics, vasodilators, calcium channel blockers, rheologic agents, prostaglandin inhibitors, anticoagulants, glucocorticoids, and free radical scavengers have had little or no effect on flap blood flow or development of necrosis (Vedder 2005). Recently promising results have been observed in experimental studies where vascular endothelial growth factor (VEGF) was given preoperatively as subdermal gene therapy in experimental skin flaps. The increase in flap blood flow caused by VEGF is thought to be mediated by nitric oxide (Huang 2006). The role of endothelin receptor antagonists in augmenting flap viability is discussed in Section 2.5.

2.6.1. Calcium antagonists and cutaneous blood flow

Calcium channel blockers are vasoactive agents capable of decreasing sympathetic tone and producing arteriolar smooth muscle relaxation. They block the adrenergically mediated vasoconstriction by inhibiting the flux of calcium ions into vascular smooth muscle cells. Whether denervation changes the effect of calcium channel blockers on vascular smooth muscle, is unknown. The density of dihydropyridine calcium channel blocker binding sites was decreased to almost one-third of its normal value after denervation in vas deferrens of rats (Jurkiewicz 1996), but in another study denervation increased the effect of calcium channel

blockers nifedipine and cobolt in slow skeletal muscles in frogs (Vasquez 2001). This topic has not been investigated in humans.

Felodipine is a vascular selective dihydropyridine calcium channel blocker with no direct effect on cardiac contractility or conduction at therapeutic dosages. It dilates peripheral resistance arterioles, but has no effect on veins. It lowers arterial blood pressure by reducing peripheral resistance without causing negative inotropic effects. Felodipine is a more powerful vasodilator than verapamil, diltiazem, or nifedipine (Ljung 1985). The dosage used in treatment of hypertension is 5–10 mg once daily. In healthy subjects, 15 mg of felodipine causes an increase in forearm blood flow and a decrease in forearm peripheral resistance (Agner 1985).

Topical nifedipine has reduced the incidence of necrosis in experimental random pattern skin flaps (Davis 1999). Oral dihydropyridine calcium antagonists have reduced the incidence of necrosis in some experimental studies (Hira 1990, Pal 1991, Yessenow 1991, Baillet 1994), but contradictory results have also been reported (Miller 1985, Emery 1990). Dihydropyridine calcium antagonists, e.g. amlodipine, felodipine, nisoldipine, and nifedipine, have been able to inhibit ET-1-induced vasoconstriction in some clinical and experimental studies (Kiowski 1991, Liu 1994). The effect of felodipine on blood flow or necrosis in flaps has not been reported before the studies presented in this thesis.

2.7. Effect of overweight on flap blood flow

2.7.1. Measurement of obesity

Body mass index

Body mass index (BMI), calculated as weight (kg)/height (m)², has traditionally been considered a reliable index of relative body weight (Keys 1972). The widely used classification of obesity based on BMI is presented in Table V (Krotkiewski 1983, Poirier 2006). Obesity is defined as BMI greater than the 85th percentile or a body weight 20 % over ideal body weight.

Severe obesity is defined as BMI greater than the 90th percentile or body weight 40 % over the ideal weight (Najjar 1987, Choban 1997).

Waist-hip circumference ratio

Body fat distribution can be described with the waist-hip circumference ratio (WHCR) (Lapidus 1984, Soler 1988). WHCR is the ratio between waist circumference and hip circumference. Waist circumference should be measured with the patient standing, at the border of the lowest third of the distance between the xiphoid process and umbilicus, and hip circumference about 4 cm below the anterior iliac spine (Lapidus 1984).

In women, upper body obesity has been associated with cardiovascular problems (Lapidus 1984) and increased peripheral vascular resistance (Jern 1992). WHCR >0.84 is considered upper body type, WHCR 0.80–0.84 medium type and WHCR <0.80 lower body type fat distribution (Soler 1988). According to the criteria of the World Health Organization (WHO), WHCR >0.9 in men and >0.85 in women denotes abdominal obesity (National Institutes of Health 1998).

Measurement of thickness of fat with ultrasonography

Ultrasonography is a convenient, noninvasive method for imaging soft tissues without radiation exposure. It has been used for measuring the thickness of subcutaneous fat (Katch 1983, Ramirez 1992, Suzuki 1993, Orphanidou 1994) and muscles (Hides 1994). The thickness of subcutaneous fat of the TRAM flap area, and its relation to cutaneous necrosis have been investigated (Yano 2003). In that study, the average subcutaneous fat thickness over the abdomen correlated with BMI. The subcutaneous fat thickness could be estimated to some extent by BMI with the exception of some patients with high BMI, who had a large amount of visceral fat but only moderate subcutaneous fat. According to the same study, abdominal fat thickness is not a risk factor for necrosis of pedicled transverse rectus abdominis musculocutaneous flaps in patients who are thin, average, or only mildly obese (Yano 2003).

2.7.2. Overweight and complications in TRAM flaps

Overweight is associated with an increased risk of comorbidities (Poirier 2006) and complications related to surgical procedures (Abdel-Moneim 1985, Choban 1997). Obesity of the patient may cause several complications at the donor site and in the flap itself, probably because of cardiovascular problems (Lapidus 1984).

High rates of flap and donor-site morbidity have been observed in obese patients who underwent breast reconstruction with a pedicled TRAM flap (Holmström 1979, Hartrampf 1987, Kroll 1989, Berrino 1991, Watterson 1995, Spear 2007). These complications include total flap loss, flap hematoma, flap seroma, mastectomy skin flap necrosis, donor-site infection, donor-site seroma, and abdominal hernia. Many authors have considered obesity a relative contraindication to breast reconstruction with a pedicled TRAM flap (Schefflan 1983a, Hartrampf 1987).

The free TRAM flap has been recommended instead of the pedicled TRAM flap for obese patients and other high-risk patients such as heavy smokers (Watterson 1995, Paige 1998, Chang 2000a). Obesity has, however, also been associated with increased complication rates in free flaps, and is suggested to be a relative contraindication to free TRAM flap reconstruction as well (Grotting 1989, Schusterman 1992, Grotting 1994, Kroll 1994, Schusterman 1994, Schusterman 1998, Selber 2006).

In a retrospective review of 936 free TRAM flap breast reconstructions, overweight (BMI 25–29,9) and obese (BMI 30–39,9) patients had significantly more flap and donor-site complications than patients with an ideal weight. However, the majority of overweight and even

obese patients were treated successfully. The authors state that the surgeon and patient must be aware of the possible association between obesity and complications. According to this study, morbidly obese (BMI >40) patients should avoid any type of TRAM flap breast reconstructions (Chang 2000b).

The outcomes of pedicled and free TRAM flaps in relation to weight were compared in a retrospective study. Of the 221 patients, 114 were obese (BMI >25,8). The overall complication rate was similar in pedicled and free TRAM flaps. An increased complication rate was observed in free TRAM flaps of severely obese (BMI ≥30,1) women and in pedicled flaps of obese (BMI 25,8–30) smokers. The overall complication rate correlated with BMI in free but not in pedicled TRAM flaps. This study indicates that both the pedicled and free TRAM flaps can be used successfully in obese patients, bearing in mind the possibility of complications (Moran 2001).

2.7.3. Overweight and cutaneous necrosis in surgical flaps

Obesity of the patient may pose a risk to the viability of the TRAM flap. The probable underlying causes are vascular problems (Lapidus 1984) and the stretch caused by the heavy flap on musculocutaneous perforator vessels nourishing the flap (Schefflan 1984). Consequently, obesity has been considered a relative contraindication to breast reconstruction by some authors (Schefflan 1983a, Hartrampf 1987, Grotting 1994).

In pedicled TRAM flaps, obesity has increased the risk of cutaneous necrosis in several studies (Berrino 1991, Moran 2001, Ducic 2005, Spear 2007), but some authors have reported

Table V. Classification of obesity based on body mass index (BMI) (weight (kg)/height (m)²).

Study	Slightly underweight	Ideal weight	Slightly overweight	Overweight	Obesity grade 1	Obesity grade 2	Obesity grade 3
Krotkiewski 1983	< 19	19–24	25–27	28–30		Obesity > 30	
Poirier 2006	< 18.5	18.5–24.9	Overweight	25–29.9	30–34.9	35–39.9	> 40

no effect (Kroll 1989). Fat necrosis has been observed in pedicled flaps of obese patients more often than in flaps of patients with ideal weight (Berrino 1991). In free TRAM flaps, the risk of cutaneous necrosis increased in some studies (Selber 2006), while other studies found no effect (Chang 2000b, Moran 2001).

In a retrospective study of 224 pedicled TRAM flaps, obese patients (BMI > 30) had an increased risk for cutaneous necrosis compared with patients with normal weight or overweight (Spear 2007). In a retrospective survey of 936 free TRAM flaps, the incidence of fat or

cutaneous necrosis was not increased in overweight and obese patients (Chang 2000b). In a retrospective comparison of outcomes of 114 pedicled and free TRAM flaps in patients with BMI > 25.8, cutaneous necrosis was more common in pedicled flaps than in free flaps. The average BMI was 30 in patients with pedicled flaps and 32 in those with free flaps. The incidence of fat necrosis was equal for both flap types (Moran 2001). Prospective studies on the effect of obesity on fat or cutaneous necrosis in TRAM flaps, except for Study V in this thesis, have not been reported.

3 Aims of the study

The purpose of this study was to obtain new knowledge about microcirculation and the TRAM flap during breast reconstruction.

The study focused on the following questions:

1. What kind of perioperative changes are measured with LDF and $P_{tc}O_2$ in the cutaneous blood flow of pedicled and free TRAM flaps for breast reconstruction (I, II)?
2. Can postoperative development of cutaneous necrosis be predicted in pedicled TRAM flaps with perioperative LDF or $P_{tc}O_2$ measurements (I)?
3. What kind of changes occur in the plasma concentrations of ET-1 during and after prolonged plastic surgical operations (TRAM flap being used as an example)? Can any association be found between the ET-1 concentrations and peripheral vasoconstriction, changes in blood pressure and heart rate, and development of cutaneous or fat necrosis (III)?
4. Can preoperatively administered felodipine, a vasodilating calcium antagonist, cause changes in plasma ET-1 release and degree of vasoconstriction perioperatively, or cutaneous blood flow and development of cutaneous necrosis in a free TRAM flap postoperatively (IV)?
5. Is there any association between the indices of obesity and the postoperative development of skin or fat necrosis in pedicled TRAM flaps (V)?

4 Patients and methods

4.1. Patients

This clinical investigation was performed on 58 women undergoing a breast reconstruction with a TRAM flap at the Department of Plastic Surgery, Helsinki University Central Hospital, in 1989–1993. The purpose and nature of the study were explained to the patients before obtaining their informed consent. The study protocols of all investigations were approved by the Ethics Committee of Töölö Hospital and the protocol of Study IV also by the Finnish National Agency for Medicines. The work consisted of five studies (I–V). The characteristics of the patients are shown in Table VI.

During Study II four patients with breast reconstruction using a “supercharged” TRAM flap, i. e. a pedicled TRAM flap with an additional anastomosis to the vessels in the thoracic area, were also evaluated.

In Study I two patients had hypertension requiring medication, and one also had hypothyreosis. In Study II, one patient took medication for hypertension and one for hypothyreosis. In Study V, one patient took aspirin and gold for rheumatoid arthritis with mild symptoms. Otherwise, all the patients were considered healthy, except for the breast cancer treated earlier.

4.2. Methods

4.2.1. Study designs

Study I

Fifteen consecutive females scheduled for breast reconstruction were enrolled in this prospective study.

Changes in the cutaneous blood flow of a pedicled TRAM flap were investigated with LDF and $P_{tc}O_2$ at ten predetermined times perioperatively and on the first, third, and seventh postoperative days (Table VII). The patients were observed for development of cutaneous necrosis during the one-week hospital stay.

Study II

In this prospective study, the cutaneous blood flow of a free TRAM flap was evaluated in 11 women with breast reconstruction. The skin blood flow was measured with LDF and $P_{tc}O_2$ at the same preoperative and intraoperative predetermined times as in Study I, and on the third postoperative day.

Measurements were also taken from the four women with a pedicled TRAM flap with an additional microvascular anastomosis of the inferior epigastric vessels.

Wound healing was observed clinically and

Table VI. Characteristics of patients in Studies I–V.

Study	I	II	III	IV	V
Number of patients	15	11	10 ¹	20	12 ¹
Age, years	46 (31–61)	46 (32–59)	47 (31–60)	46 (34–59)	9 (31–60)
Weight, kg	64 (52–76)	66 (52–85)	65 (47–74)	64 (50–85)	63 (47–74)
Height, cm	163(158–173)	165 (160–175)	164 (147–171)	164 (156–169)	163 (147–171)
Time from mastectomy, years	4.8(1,5–7)	6.2(2–19)	4.2 (2,5–11)	N/A	3.7(2,5–11)
Duration of operation, minutes.	284(225–330)	396(312–510)	282 (230–360)	291(225–460)	280(230–360)
Smokers	1/15	0/11	2/10	7/20	1/12

¹Nine of the patients were the same in Studies III and V. N/A Not reported. The data are represented as arithmetic means (range).

an ultrasound investigation was performed on the reconstructed breast during the hospital stay in order to detect any signs of fat necrosis.

Study III

Ten women undergoing a pedicled TRAM flap reconstruction were investigated in a prospective manner in order to determine whether plasma ET-1 concentration has any role in the vasoconstriction that develops during long-lasting operations. Plasma ET-1 concentrations, forearm-finger temperature gradient (T_{grad}), rectal temperature (T_{rect}), mean arterial pressure (MAP,) and heart rate (HR) were measured at nine predetermined times before, during, and after the operation (Table VIII). Wound healing was observed in the same way as in Study II.

Study IV

The effect of felodipine on plasma ET-1 levels, peripheral vasoconstriction, and flap survival was examined in a randomized, double-blind, and prospective setting in 20 women scheduled for breast reconstruction with a free TRAM flap. The patients were randomly allocated to receive either felodipine (Plendil® Astra Zeneca, Sweden) 5 mg or a placebo tablet perorally on the preoperative evening and in the morning before the operation. The baseline

values of MAP and HR were measured, and a blood sample was drawn for plasma ET-1 determination on the preoperative day on the ward. T_{grad} , MAP, and HR were measured and blood for ET-1 determination was sampled on the operation day at the same measuring times as in Study III (Table VIII). Postoperatively, on the ward, blood was sampled for plasma ET-1 determinations on the first, second, and sixth postoperative days. To assess cutaneous blood flow of the TRAM flap area, $P_{tc}O_2$ was measured on the flap marked on the abdominal skin preoperatively and one hour after arrival in the recovery room, on the first, second, and sixth postoperative days on the flap at its final site. All measurements were performed on the ipsilateral (the side with the rectus muscle) and contralateral sides of the vertical skin area of the flap. Wound healing was observed clinically.

Study V

The association of degree and type of obesity with outcome of the pedicled TRAM flaps for breast reconstruction was evaluated in 12 women. The study was planned to be performed partly on the same patients as in Study III. One of the ten patients in Study III refused to take part in Study V, and so nine patients were the same in Studies III and V.

Table VII. The Laser Doppler flowmetry (LDF) and $P_{tc}O_2$ measuring times in Studies I and II.

Phase	Measuring time	LDF ipsilaterally	LDF contralaterally	$P_{tc}O_2$ ipsilaterally.	$P_{tc}O_2$ contralaterally
1	On preoperative day			I, II	I, II
2	Patient anesthetized, before incision	I, II	I, II	I, II	I, II
3	Contralateral side of flap elvated	I, II	I, II		I, II
4	Whole flap elevated and rectus muscle cut	I, II	I, II		I, II
5	Inferior epigastric artery ligated (I) or superior pedicle ligated (II)	I, II	I, II		I, II
6	Inferior epigastric vein ligated (I) or flap on the chest, before anastomosis (II)	I, II	I, II		I, II
7	Recovery room	I, II	I, II	I, II	I, II
8	On first postoperative day (I) On third postoperative day (II)	I II	I II	I II	I II
9	On third postoperative day	I	I	I	I
10	On seventh postoperative day	I	I	I	I

On the preoperative day, weight was estimated by measuring body mass index (BMI), and type of body fat distribution by waist-hip-circumference ratio (WHCR). Thickness of the abdominal fat over the rectus muscle was measured by ultrasonography on the preoperative day and at one week, six weeks, three months, and nine months postoperatively.

Survival of the TRAM flaps was evaluated clinically during the hospital stay and at the outpatient visits at the same time-points as the ultrasonography measurements were made. Signs of fat necrosis were noted during the ultrasonography investigations.

4.2.2. Anesthetic management

The patients were operated on under general anesthesia as recommended for microvascular and flap surgery at the time of Studies I–V (Robins 1983, Macdonald 1985). The patients were premedicated with 10 mg of diazepam approximately 75 minutes before induction of anesthesia. After intravenous boluses of fentanyl 0.1 mg, glycopyrronium 0.2 mg, and precurarization with pancuronium 1 mg, anesthesia was induced with thiopentone 5 mg/kg. Suxamethonium 1–1.5 mg/kg was adminis-

tered to facilitate tracheal intubation. Anesthesia was maintained with 65 % inhaled nitrous oxide and 0.2–1 % isoflurane in oxygen. The aim was to maintain systolic blood pressure at 100–110 mmHg during dissection of the flap and at about 120 mmHg after the flap had been transferred to the mastectomy wound and/or the anastomoses were finished. The lungs were ventilated mechanically to normocapnia (exhaled end-tidal carbon dioxide concentration at about 5 %) with a Servo 900 ventilator (Siemens-Elema, Sweden). Neuromuscular block was produced with pancuronium 1–2 mg as needed after a bolus of 0.08 mg/kg. Fentanyl was given in doses of 0.05–0.1 mg. At the end of the operation, neuromuscular block was antagonized with neostigmine 2.0 mg and glycopyrronium 0.4 mg. Isoflurane and nitrous oxide inhalation were discontinued after the wounds had been bandaged. The trachea was extubated when spontaneous ventilation was adequate.

Hydroxyethyl starch 120 6 % (Plasmafusin, Leiras-Kabi Infusion Oy, Vantaa, Finland) (500 ml) was given after induction, and Ringer's acetate was infused to maintain a stable hemodynamic state and mild hypervolemic hemodilution. Hematocrit (packed cell volume) was kept at 0.30–0.35, and transfusion was given as needed. Dextran 40 (1000 ml) (Rheomacro-

Table VIII. The measuring times in Studies III and IV.

Phase (Study III)	Measuring time	ET-1	T _{grad}	T _{rect}	MAP	HR	P _{tc} O ₂
	On preoperative day	IV			IV	IV	IV
1	Before induction of anesthesia	III, IV	III, IV		III, IV	III, IV	
2	1 hour after induction of anesthesia	III, IV	III, IV	III, IV	III, IV	III, IV	
3	3 hours after induction of anesthesia	III, IV	III, IV	III, IV	III, IV	III, IV	
4	At end of operation	III, IV	III, IV	III, IV	III, IV	III, IV	
5	10 minutes after arrival in recovery room	III, IV	III, IV	III, IV	III, IV	III, IV	
6	30 minutes after arrival in recovery room	III, IV	III, IV	III, IV	III, IV	III, IV	
7	1 hour after arrival in recovery room	III, IV	III, IV	III, IV	III, IV	III, IV	IV
8	2 hours after arrival in recovery room	III, IV	III, IV	III, IV	III, IV	III, IV	
9	3 hours after arrival in recovery room	III, IV	III, IV	III, IV	III, IV	III, IV	
	On first postoperative day	IV					IV
	On second postoperative day	IV					IV
	On sixth postoperative day	IV					IV

dex, Kabi Infusion A/S, Norway) was infused after the operation until the next morning. All infusions were given via venous cannulas in the upper extremity on the side opposite the operative side.

Intraoperative heat loss was prevented by warming the infusion bags in water at 37 °C before the infusion started. Ambient temperature was maintained at approximately 22–24 °C during the operation and in the recovery room. Skin-surface warming devices were not used during operation, except for a water-filled warming mattress intraoperatively.

In the recovery room, the patients breathed room air during the measurements in Studies I and II. At all other times the patients breathed 35 % oxygen via a face mask in the recovery room. Oxycodone in intravenous doses of 0.05 mg/kg was given for pain relief. The need for pain medication was assessed by experienced anesthesia nurses. No other medication was given in the recovery room. On the ward pre-operatively and postoperatively, the patients breathed room air. Analgesics were given as needed on the postoperative days.

Electrocardiogram, heart rate, intra-arterial pressure, pulse oximetry, urinary output, end-tidal carbon dioxide concentration, and inspiratory oxygen concentration were monitored continuously throughout the anesthesia. Neuromuscular block was monitored with a nerve stimulator. A cannula was inserted in the radial artery of the arm with the infusion cannula for continuous blood pressure monitoring and for taking blood samples.

4.2.3. Surgical technique

The same surgeon (SAS), as the head of the team, elevated all the flaps using a standardized technique and performed all the anastomoses in free flaps. The flap was designed and drawn on the skin surface on the preoperative day. All TRAM flaps were formed of the rectus muscle and vessels opposite to the mastectomy side and a symmetric elliptic area of skin and subcutis around and below the umbilicus. The height of the skin island varied from 11 to 14 cm, the upper border of the flap being slightly above

the umbilicus and the lower border above the suprapubic area. A schematic representation of the surgical procedures is provided in Figure 2 at the Review of the Literature section.

Pedicled TRAM flaps (I, III, V)

The rectus muscle and pedicle on the opposite side to the mastectomy area were used. The half of the flap situated contralaterally to the rectus abdominis muscle and mainly below the umbilicus was first elevated as far as the linea alba. The ipsilateral (over the rectus muscle) side of the TRAM flap was then dissected, leaving three centimetres of the anterior rectus sheath on the flap. The rectus abdominis muscle was cut above the arcuate line. At this stage, the flap had a double circulation through the inferior and the superior epigastric vessels. Next, the DIEA was ligated and then the vein. The flap was tunnelled under the upper abdominal skin to the mastectomy wound. The breast was shaped by rotating the flap 180 °C so that the medial side of the breast represented the random side of the flap. The distal portion of the random side (zone IV) was discarded. The abdominal wall was reconstructed without foreign material using nonabsorbable continuous sutures to the fascia.

Free TRAM flaps (II, IV)

The rectus muscle and pedicle on the opposite side to the mastectomy area were used. The contralateral side of the flap was first elevated to the linea alba. The ipsilateral side (situated over the rectus muscle) of the TRAM flap was then dissected. Next, 2.5 cm of the anterior rectus sheath and 5 cm of the rectus muscle were taken above the arcuate line to the flap. A lateral strip (1.5 cm in width) of the rectus muscle was left in place to avoid contraction of the muscle edges. The rectus muscle was cut below the deep inferior epigastric pedicle. The rectus muscle was then cut at a level below the umbilicus, and the superior epigastric pedicle was ligated. The DIEA was dissected down to the external iliac vessels. The pedicle was about 8 cm long. The deep inferior epigastric vessels were then ligated, and the flap was without perfusion. The abdominal wall was closed by nonabsorbable sutures. The assistant dissected

the scar at the chest wall and the skin to the inframammary fold.

The recipient vessels in the axilla were exposed. The deep inferior epigastric pedicle was anastomosed end-to-end either to the thoracodorsal vessels or to the scapular circumflex vessels. The free TRAM flap was placed on the chest wall, the umbilicus caudally and the contralateral side of the flap side medially. Excessive skin and subcutis were removed, and the breast was shaped.

Pedicated TRAM flaps with the additional microvascular anastomosis (II)

These four pedicated TRAM flaps were elevated in the same way as the regular pedicated TRAM flaps, and the deep inferior epigastric pedicle was dissected and ligated (phase 5a). The flap was pulled to the thoracic wall (phase 6). The inferior epigastric vessels were anastomosed end-to-end to the thoracodorsal vessels (3 cases) or the scapular circumflex vessels (1 case) in the axilla.

4.2.4. Measurements

Cutaneous blood flow

The cutaneous blood flow of the TRAM flap was monitored with LDF in Studies I and II

and with $P_{tc}O_2$ in Studies I, II, and IV. The inspired oxygen concentration was 21 % during the pre- and postoperative LDF and $P_{tc}O_2$ measurements, 35 % intraoperatively, and 60 % during an oxygen stimulation test in Study I. Sterility of the LDF and $P_{tc}O_2$ probes was maintained during the operation.

LDF (I, II)

The LDF values were measured with a laser Doppler flowmeter (Periflux 2B, Perimed, Stockholm, Sweden) at times shown in Table VII. A standard probe was used. One probe holder was attached with a double-sided sticker on the axial (ipsilateral) side and one on the random (contralateral) side of the flap skin, both the same distance from midline, approximately 5–7 cm depending on the form of the flap (Fig. 7). Each measurement lasted for at least 10 minutes.

The measurements were made at the predetermined times shown in Table VII. The first measurement was performed after the patient had been anesthetized. The probe holders were then detached during skin disinfection and later attached at exactly the same sites. After this the probe holders remained attached at the sites until the last measurement on the third (II) or the seventh (I) postoperative day.

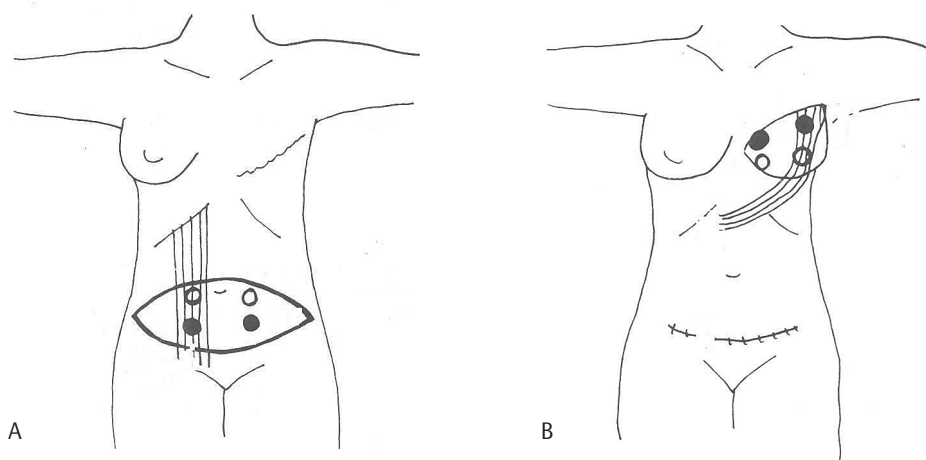


Figure 7. LDF and $P_{tc}O_2$ measurement sites on the TRAM flaps, with the flap at its original site (A) and on the chest (B). The black circles represent the sites of the LDF probes and the white circles the sites of the $P_{tc}O_2$ probes. The measuring sites were the same in free and in pedicated (in this picture) TRAM flaps.

$P_{tc}O_2$ (I, II, IV)

$P_{tc}O_2$ of the TRAM flap skin was measured with a transcutaneous oximeter (Transcom 807, Novamatrix Medical Systems, Inc., CT, USA). The measurement sites were on the ipsilateral side, over the rectus muscle of the TRAM flap, and on the contralateral side of the flap, about 1 cm cranially to the LDF measurement sites on both sides of the flaps (Fig. 7).

The measurements were made using one probe, which was moved to the other measuring sites according to the study protocol. Before the first measurement and before each replacement, the $P_{tc}O_2$ probe was calibrated against an oxygen-free zero solution and ambient pressure. The temperature of the probe was 43.5 °C. The skin seemed to tolerate the heating well since no burn injuries were observed on the skin under the probe.

In Studies I and II, the $P_{tc}O_2$ measurements were performed at the times shown in Table VII. On the operation day, the ipsilateral and contralateral values were obtained after the patient was anesthetized (phase 2) and in the recovery room. Between phases 2 and 7, the $P_{tc}O_2$ probe was left on the contralateral side and kept in place. The ipsilateral values were not measured from phase 3 to phase 6 due to the time-consuming calibration needed before each replacement of the probe. After the operation, the $P_{tc}O_2$ values were taken from both sides of the flap.

In Study IV, $P_{tc}O_2$ was measured from the ipsilateral and contralateral sides of the TRAM flap at the times shown in Table VIII.

An oxygen stimulation test was performed in Study I after each postoperative measurement, with the patient breathing 60 % oxygen for 15 minutes. A minimum rise of 50 % in the $P_{tc}O_2$ value was considered a positive result in the oxygen test.

Temperature measurements (I–IV)

Rectal and peripheral temperatures were measured with thermocouple probes (Exacon MC 8700, Exacon, Copenhagen, Denmark). The patients had received laxatives to empty the rectum for the surgery. After induction of anesthesia, the rectal temperature (T_{rect}) probe

was inserted about 10–15 cm and taped in place. In Studies I and II, the peripheral temperature (T_{periph}) was measured from the index finger of the mastectomy side. In studies III and IV, probes for skin temperature measurements were attached on the radial side of the middle third of the antebrachium (T_{ant}) and on the tip of the index finger (T_{ind}) of the arm on the mastectomy side. No intravenous fluids were infused in the arm with the peripheral temperature probes.

The baseline values of T_{rect} were recorded immediately after the induction of anesthesia, and the baseline values of the peripheral temperatures (T_{periph} , T_{ant} and T_{ind}) before the induction of anesthesia.

In Studies I and II, T_{rect} and T_{periph} were measured continuously during the operation. The values at phases 2 and 6 and at the end of the operation were included in the study. In Studies III and IV, the thermoregulatory vasoconstriction was evaluated as the temperature gradient (T_{grad}) between T_{ant} and T_{ind} ($T_{ant} - T_{ind}$) (Stoen 1990). T_{grad} was measured continuously during the operation, and the perioperative values were included in the studies as shown in Table VIII. T_{grad} exceeding 4 °C was considered significant degree of vasoconstriction.

The arm on the mastectomy side was covered with a cotton sheet during the operation. The rest of the patient was covered with double-thickness cotton drapes. In the recovery room, the arm with the measurement probes was exposed; otherwise, the patient was covered with a hospital blanket and a sheet.

Plasma ET-1 determinations (III, IV)

In Studies III and IV, blood samples for ET-1 determinations were taken at the times shown in Table VIII. In Study III, before induction of anesthesia, a 16 G venous cannula was inserted without local anesthesia into a cubital vein of the arm on the side of the removed breast to obtain blood for the plasma ET-1 determinations. The cannula was closed with an obturator while not in use. In Study IV, on the preoperative day on the ward, a venous blood sample was drawn from the cubital vein for plasma ET-1 determination before the blood pressure measurement. In the perioperative period, ar-

terial blood samples for ET-1 determinations were collected at the times shown in Table VIII. In Study IV, samples for the ET-1 determinations were obtained from venous blood on the postoperative days.

Ten milliliters of blood was drawn into ice-chilled tubes containing 15 mM (final concentration) Na₂EDTA and carried immediately to the laboratory. Plasma was separated by centrifugation at 8 °C and stored at -70 °C until assayed for ET-1.

Radioimmunoassay of ET-1 was performed as described earlier (Fyhrquist 1990) using ET-1 and ET-1 antiserum generated in rabbits. The antiserum showed 100 % cross-reaction with ET-2 and ET-3 and <0.1 % cross-reaction with the 20–50, 74–91, and 171–201 sequences of preproendothelin and with big ET-1, sequences 1–38 and 33–38.

Before ET-1 radioimmunoassay, plasma samples were purified using Bondelut C18-OH analytical columns. One milliliter of plasma was acidified with 4 % acetic acid and applied on a column. After the samples had been washed with distilled water, the absorbed peptide was eluted with 40 % ethanol and 4 % acetic acid. The eluted fraction was lyophilized and dissolved into assay buffer, 50 mM buffer pH 7.4, containing 1 mM Na₂EDTA, 0.2 mM cystine, 0.01 % merthiolate, 0.1 % bovine serum albumin, and 0.1 % triton x-100. Radioimmunoassay was performed using sequential incubation by adding I¹²⁵-labelled ET-1 on the third day. Bound ligands were separated on the fourth day using the second antibody technique. The sensitivity of the assay was 0.8 pg / tube, and the recovery of ET-1 added to plasma was 80 %. For external control, in each ET-1 radioimmunoassay three samples of pooled normal human plasma containing 0, 20, or 50 pg of human ET-1 were measured.

Hemodynamic measurements and other blood samples (I–IV)

HR and MAP values registered at the times shown in Table VIII were included in Studies III and IV. On the preoperative day on the ward, blood pressure (noninvasive blood pressure monitor) and HR were measured with the patient seated. The perioperative MAP values

were obtained from the indwelling catheter in the radial artery.

Blood was sampled for arterial oxygen tension (PaO₂) determinations in Study I at phase 3, three hours after the induction of anesthesia, in the recovery room, and during the oxygen stimulation test. In Study II, PaO₂ was determined at phases 3 and 7. In Study III, arterial samples for PaO₂ determinations were taken one and three hours after induction of anesthesia and 30 minutes after arrival in the recovery room, and in Study IV three hours after induction and 30 minutes and two hours after arrival in the recovery room.

Blood for hematocrit determinations was sampled in all studies as needed to maintain the desired level of hemodilution. In Study III, the hematocrit values determined at the same times as PaO₂, and in Study IV the values obtained preoperatively and two hours after arrival in the recovery room were included in the study.

Assessment of weight (V)

On the preoperative day, the weight and the type of body fat distribution was estimated by measuring BMI and WHCR. BMI is calculated as weight (kg) / height² (m). WHCR is the ratio between waist circumference and hip circumference. Waist circumference was measured with the patient standing, with a tape measure, at the border of the lowest third of the distance between the xiphoid process and umbilicus, and hip circumference was measured about 4 cm below the anterior iliac spine (Lapidus 1984).

Thickness of the abdominal fat and the rectus abdominis muscle of the flap area were measured by ultrasonography. All ultrasonography measurements were made by the same radiologist. Aloka SSD 500 ultrasonography equipment (Aloka Co. Ltd., Japan) with a 7.5 MHz surface probe was used for the measurements. The margins of the TRAM flap were drawn on the abdominal skin on the preoperative day. The ipsilateral side of the flap was divided into five equally long segments on its long axis, and the thickness of the subcutaneous fat was measured at these four points. The maximal thickness of the underlying rectus

abdominis muscle on the ipsilateral side was measured at three points: on the top and bottom margins of the flap and at the midpoint between them. Postoperatively, the same measurements were made at one week, six weeks, three months, and nine months, at the same sites of the flap, and the patients were interviewed and examined. Possible complications were also analyzed. A clearly increased signal intensity of the fat tissue in ultrasonography was regarded as a sign of fat necrosis.

4.2.5. Statistical analyses

Studies I and II

The LDF values were obtained in arbitrary units. Because of the wide variation between LDF values measured from different persons and different sites of the same person (Tenland 1982), the LDF values taken at each site are presented as a percentage of the reference value of that measuring site. The values measured at phase 2 (I, II) are regarded as the reference values of the LDF and $P_{tc}O_2$ measurements.

The measured values are expressed as mean \pm SEM (I) or mean \pm SD (II). The statistical significance of differences between means was tested using Student's t-test for dependent and independent series (I). The statistical differences between the measuring times within one group were analyzed with the nonparametric Wilcoxon-Pratt test. Differences between the free TRAM flaps and the pedicled TRAM flaps with additional anastomosis were tested with a two-sample rank-sum test (Mann-Whitney test) (II).

Study III

Parametric data are given as mean \pm SD and nonparametric data as median (25–75 % quartiles). The statistical analysis for differences between the measuring times was performed with the Wilcoxon-Pratt test. Nonlinear correlation between measured parameters was tested with the Spearman rank test.

Study IV

The data are given as means (95 % confidence intervals (CI)). Characteristics of the patients are given as means (range). For comparison between the groups at each measuring time, differences of means (95 % CIs) were calculated. Statistical significance was tested with the pooled variance t-test.

Study V

Patients were divided into groups depending on the BMI and WHCR as follows: BMI < 19 = slightly underweight; BMI 19–24 = ideal weight; BMI 25–27 = slightly overweight; and BMI 28–30 = moderately overweight (Krotkiewski 1983), and WHCR < 0.80 = lower body type; WHCR 0.80–0.84 = medium type; and WHCR > 0.84 = upper body type fat distribution (Soler 1988).

Abdominal fat thickness of each patient at every measuring time was calculated as a mean of the four measurements taken. The significance of differences between the groups was tested with the Chi-square test. Statistical analysis of differences in the measured variables between the measurement times was made with the Wilcoxon-Pratt test and for differences between the patients with and without necrosis with the Mann-Whitney test. P values of less than 0.05 were considered significant.

5 Results

5.1. Perioperative changes of cutaneous blood flow in TRAM flaps (I, II)

One patient was excluded from Study I because of technical problems in her LDF measurements. Thus, the measurements of 14 patients are presented in this study. In Study II, there were technical problems in the LDF measurements of one patient and her LDF measurements were therefore excluded from the study. Other measurements in Study II are from all the 11 patients.

5.1.1. Cutaneous blood flow in pedicled TRAM flaps (I)

LDF values

The changes in LDF values at the contralateral and ipsilateral measurement sites of the pedicled TRAM flaps are shown in Figure 8.

Elevation of the contralateral side of the TRAM flap (phase 3) caused a significant increase in the ipsilateral value from base-

line level (phase 2). When the whole flap was elevated and the inferior part of the rectus muscle cut (phase 4), the blood flow returned to baseline level on both sides. After ligation of the inferior epigastric artery (phase 5), the contralateral LDF value decreased significantly to $57 \pm 8 \%$ ($p < 0.001$) and the ipsilateral value to $78 \pm 11 \%$ of baseline level. Ligation of the vein (phase 6) did not cause a change from phase 5 in LDF values. In the recovery room (phase 7), the LDF values were contralaterally low, $62 \pm 8 \%$ ($p < 0.01$) of the reference value, and ipsilaterally near baseline level. On the first (phase 8), third (phase 9), and seventh (phase 10) postoperative day, the LDF values were near baseline level on contralateral and ipsilateral sides of the flap.

$P_{tc}O_2$ values

The $P_{tc}O_2$ values at the contralateral and ipsilateral measurement sites of the pedicled TRAM flaps are shown in Figure 9.

On the preoperative day (phase 1), $P_{tc}O_2$ was 48 ± 3 mmHg on the contralateral and

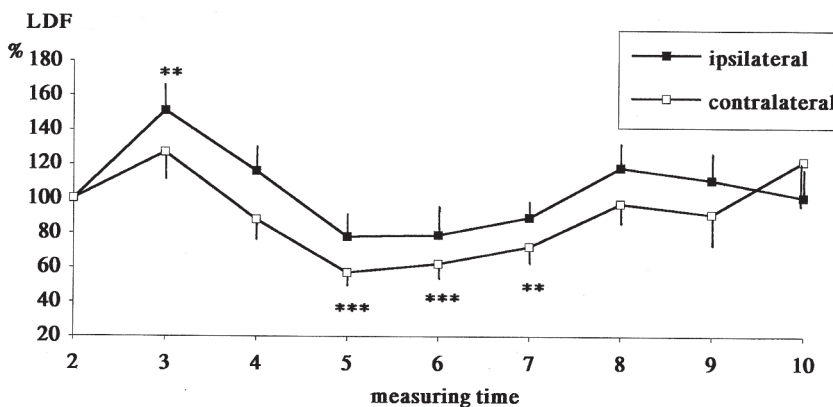


Figure 8. LDF values as a percentage of the initial value (phase 2) on the ipsilateral and contralateral sides of the 14 pedicled TRAM flaps. ** represents $p < 0.01$ and *** $p < 0.001$ for difference from the initial value on each side of the flap. Measuring times as in Table VII. Values represent mean \pm SEM.

44 ± 4 mmHg on the ipsilateral side the flap. When the patient was anesthetized (phase 2), $P_{tc}O_2$ increased significantly contralaterally and ipsilaterally. $P_{tc}O_2$ was measured only contralaterally between phases 2 and 7. When the contralateral side of the flap was elevated, the contralateral $P_{tc}O_2$ returned to 37 ± 8 mmHg. It decreased significantly compared with the baseline to 17 ± 5 mmHg when the whole flap was elevated and the rectus muscle cut (phase 4). When the pedicle artery (phase 5) and vein (phase 6) were cut, contralateral $P_{tc}O_2$ stayed

at 5 ± 2 mmHg. In the recovery room (phase 7), the contralateral $P_{tc}O_2$ was 5 ± 2 mmHg and ipsilateral $P_{tc}O_2$ 11 ± 3 mmHg. On the first (phase 8), third (phase 9), and seventh (phase 10) postoperative day, the contralateral and ipsilateral $P_{tc}O_2$ values were low, but increased slowly towards the end of the study period. During phases 7, 8, 9, and 10 the ipsilateral $P_{tc}O_2$ values were significantly higher than the contralateral values. All values measured during phases 4–10 differed significantly from the initial contralateral and ipsilateral values.

Stable oxygenation of the patients was maintained throughout the operation. PaO_2 was 171 ± 7 mmHg one hour after induction of anesthesia, 173 ± 6 mmHg three hours after the induction, 80 ± 4 mmHg in the recovery room with the patient breathing room air, and 271 ± 27 mmHg in the recovery room during the oxygen stimulation test.

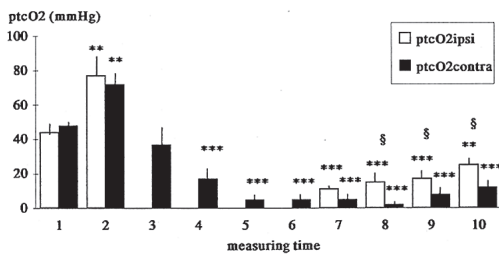


Figure 9. Changes in transcutaneous oxygen tension ($P_{tc}O_2$) at the ipsilateral and contralateral measurement sites of the 14 pedicled TRAM flaps. ** represents $p < 0.01$ and *** $p < 0.001$ for difference from the initial value (phase 1) on each side of the flap. \$ represents $p < 0.01$ for differences between the ipsilateral and contralateral sides at each measuring time. Measuring times as in Table VII. Values represent mean ± SEM.

5.1.2. Cutaneous blood flow in free TRAM flaps (II)

LDF values

Changes in LDF values on the contralateral and ipsilateral measurement sites of the free TRAM flaps are shown in Figure 10.

Elevation of the contralateral side of the TRAM flap (phase 3) caused an increase in the

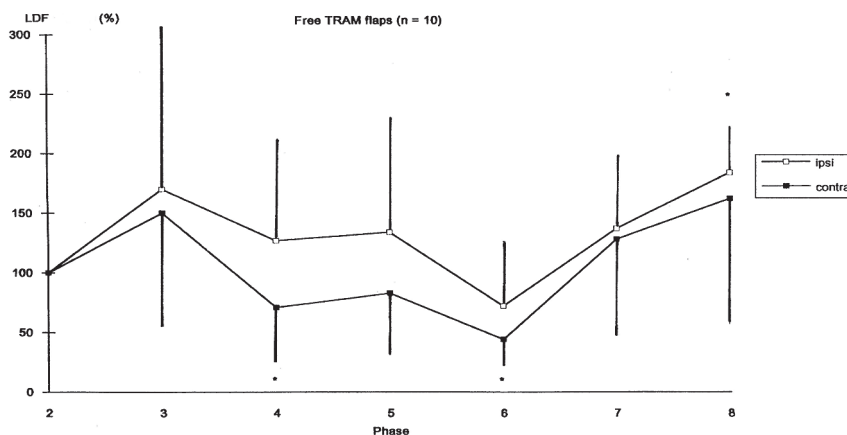


Figure 10. LDF values as a percentage of the initial value (phase 2) at the ipsilateral and contralateral measuring sites of 10 free TRAM flaps. * represents $p < 0.05$ for differences from the initial value on each side of the flap. Measuring times are as in Table VII. Values are given as mean ± SD.

contralateral and ipsilateral LDF levels. When the whole flap was elevated and the inferior part of the rectus muscle cut (phase 4), the blood flow decreased contralaterally significantly compared with phase 2 to $71 \pm 45\%$ of the initial value ($p < 0.05$) and remained ipsilaterally at $127 \pm 85\%$. After ligation of the superior epigastric pedicle (phase 5), the LDF values remained stable. When the inferior pedicle was also cut and the flap was without circulation and lifted to the chest (phase 6), the LDF value decreased contralaterally significantly to $44 \pm 23\%$ ($p < 0.05$) and ipsilaterally to $72 \pm 56\%$. In the recovery room (phase 7), the LDF values had returned to the baseline level. On the third (phase 8) postoperative day,

the LDF values had increased further, contralaterally to $162 \pm 101\%$ and ipsilaterally significantly to $184 \pm 41\%$ ($p < 0.05$).

$P_{tc}O_2$ values

The $P_{tc}O_2$ values at the contralateral and ipsilateral measurement sites of the 11 free TRAM flaps are shown in Figure 11.

The preoperative $P_{tc}O_2$ was contralaterally 55 ± 8 mmHg and ipsilaterally 52 ± 10 mmHg (phase 1). After induction of anesthesia (phase 2), $P_{tc}O_2$ increased significantly both contralaterally and ipsilaterally. After elevation of the contralateral side of the flap (phase 3), the contralateral $P_{tc}O_2$ fell to the initial level. The ipsilateral $P_{tc}O_2$ was not measured in phases 3–6. The contralateral $P_{tc}O_2$ decreased to 26 ± 29 mmHg when the whole flap was dissected and both pedicles were intact (phase 4). When the flap was without perfusion in phase 6, the contralateral $P_{tc}O_2$ fell to 2 ± 2 mmHg ($p < 0.05$). In the recovery room (phase 7), the contralateral $P_{tc}O_2$ was 21 ± 18 mmHg ($p < 0.05$) and the ipsilateral $P_{tc}O_2$ 43 ± 27 mmHg. On the third postoperative day the contralateral and ipsilateral $P_{tc}O_2$ was still low compared with the baseline values.

The LDF and $P_{tc}O_2$ values of the four patients with the pedicled TRAM flap and an additional microvascular anastomosis in Study II are given in Table IX. There were too few patients for us to be able to draw any statistical conclusions.

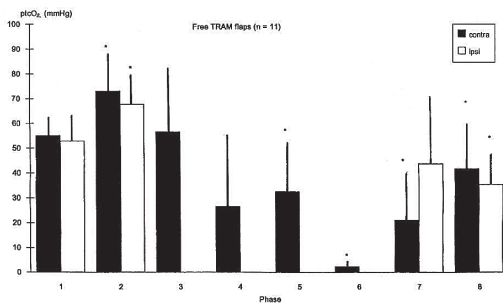


Figure 11. Transcutaneous oxygen tension ($P_{tc}O_2$) at the ipsilateral and contralateral measuring sites of 11 free TRAM flaps. * represents $p < 0.05$ for differences from the initial value on each side of the flap. Measuring times are as in Table VII. Values are given as mean \pm SD.

Table IX. Contralateral and ipsilateral LDF and $P_{tc}O_2$ values of the patients with a pedicled TRAM flap with an additional microvascular anastomosis ($n = 4$). Values are given as mean \pm SD.

	LDF (% of initial value)		$P_{tc}O_2$ (mmHg)	
	contra	ipsi	contra	ipsi
Phase 1			51 \pm 6	45 \pm 1
Phase 2	100	100	64 \pm 26	42 \pm 24
Phase 3	260 \pm 255	163 \pm 47	47 \pm 37	
Phase 4	77 \pm 56	83 \pm 21	14 \pm 16	
Phase 5a	54 \pm 30	73 \pm 30	10 \pm 18	
Phase 6	77 \pm 59	76 \pm 17	0 \pm 0	
Phase 7	236 \pm 258	93 \pm 36	20 \pm 18	23 \pm 13
Phase 8	145 \pm 70	158 \pm 56	19 \pm 13	32 \pm 4

5.2. Prediction of cutaneous necrosis in pedicled TRAM flaps (I)

During the hospital stay eight of the 14 patients with pedicled TRAM flaps developed cutaneous necrosis, which was diagnosed clinically. The width of the necrosis varied between 5 and 50 mm. The two patients with a 50-mm-wide skin necrosis had other complications. One had a postoperative deep vein thrombosis, and liver metastases were detected later by ultrasonography. The other patient had received radiotherapy for spinal metastases three years earlier. On the postoperative days, she had marked postoperative atelectasis. Both of these patients were taking tamoxifen preoperatively. Three of the eight patients with skin necrosis needed a surgical revision. The smaller areas of necrosis healed spontaneously. No significant differences existed between the patients with and without necrosis with regard to age, weight, height, duration of operation, transfusions needed, or hemoglobin or arterial oxygen

tension values. The only patient who smoked did not develop necrosis.

LDF values

The LDF values in the patients with and without necrosis are shown in Figure 12.

The contralateral LDF values were significantly lower in the TRAM flaps with necrosis than in the flaps healing without complications in phase 5 ($43 \pm 7\%$ vs. $74 \pm 7\%$, respectively, $p < 0.01$), phase 6 ($50 \pm 6\%$ vs. $76 \pm 8\%$, $p < 0.01$) and phase 8 ($82 \pm 8\%$ vs. $114 \pm 11\%$, $p < 0.01$). The contralateral LDF values were lower in the necrosis group than in the non-necrosis group also during phases 3, 4, 7, 9, and 10, but the changes were not statistically significant.

The ipsilateral LDF values were significantly lower in the necrosis group than in the patients without necrosis during phase 5 ($69 \pm 1\%$ vs. $90 \pm 9\%$, respectively, $p < 0.05$) and phase 7 ($78 \pm 12\%$ vs. $101 \pm 5\%$, $p < 0.01$). No statistically significant changes occurred during phases 3, 4, 6, 8, 9, and 10.

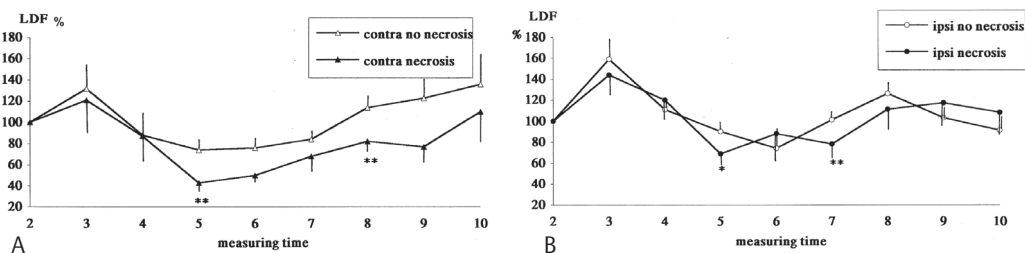


Figure 12. LDF levels as a percentage of the initial value (phase 2) at the contralateral (A) and ipsilateral (B) measuring sites of the 14 pedicled TRAM flaps in patients with and without necrosis. * represents $p < 0.05$ and ** $p < 0.01$ for difference between the patients with and without necrosis at each measuring time. Measuring times as in Table VII. Values are given as mean \pm SEM.

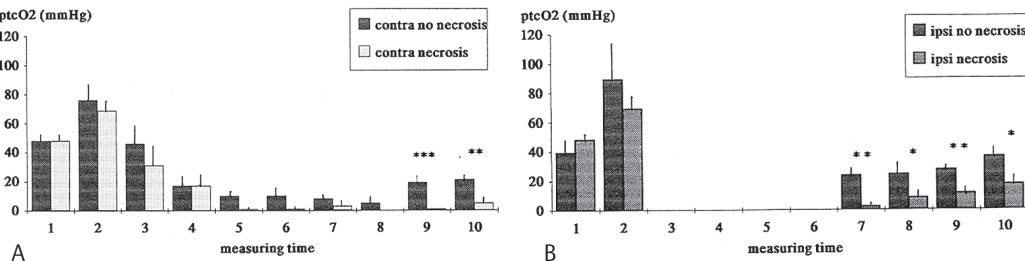


Figure 13. Changes in $P_{tc}O_2$ at the contralateral (A) and ipsilateral (B) measuring sites of the 14 pedicled TRAM flaps in patients with and without cutaneous necrosis. * represents $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$ for difference between the patients with and without necrosis at each measuring time. Measuring times as in Table VII. Values are given as mean \pm SEM.

P_{tc}O₂ values

The P_{tc}O₂ values in the patients with and without necrosis are shown in Figure 13.

The contralateral P_{tc}O₂ values were near zero after ligation of the artery (phase 5) in the flaps with necrosis and at a slightly higher level in flaps without necrosis. The P_{tc}O₂ values in the necrosis group were significantly lower than in the necrosis group during phase 9 (1 ± 0 mmHg vs. 19 ± 4 mmHg, respectively) and phase 10 (5 ± 3 mmHg vs. 21 ± 2 mmHg) (Fig. 13 A).

The ipsilateral P_{tc}O₂ values were significantly lower in the necrosis group than in the patients without necrosis during phase 7 (2 ± 2 mmHg vs. 23 ± 4 mmHg, respectively), phase 9 (11 ± 3 mmHg vs. 27 ± 2 mmHg), and phase 10 (17 ± 5 mmHg vs. 36 ± 5 mmHg (Fig. 13 B).

The oxygen challenge test was done at phases 7–10. The oxygen test was more often negative on the contralateral side of flaps developing cutaneous necrosis than in flaps without necrosis, but the difference was not statistically significant. In the two patients with a 50-mm-wide necrosis, the oxygen test was negative on both sides of the flap in all but one measurement.

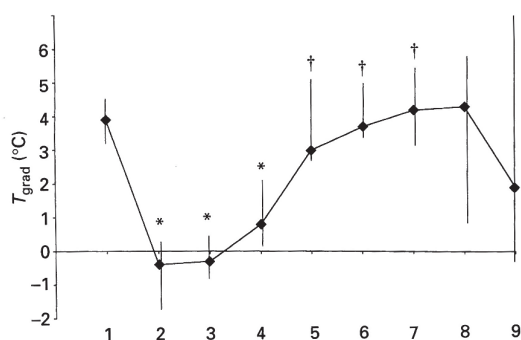


Figure 14. Perioperative changes in forearm-finger temperature gradients (T_{grad}) (difference between the skin temperatures of the antebrachium and index finger of the same arm). Values are given as median and 25–75 % percentiles. * represents $p < 0.05$ compared with values measured before induction and † $p < 0.01$ compared with values at the end of the operation. Measurement times as in Table VIII.

5.3. Relation of plasma ET-1 concentrations to peripheral vasoconstriction, blood pressure, heart rate, and cutaneous or fat necrosis (III)

Plasma ET-1 concentrations

In one of the ten patients in Study III, the plasma ET-1 levels were exceptionally high at the three measurement times. Her highest ET-1 concentration was 51 pg/ml, 7–22 standard deviations above the mean of the plasma ET-1 levels of the other patients. A technical error in handling her ET-1 samples was suspected, and thus all data for this patient were excluded. The patient was a nonsmoker who had had a mastectomy three years earlier and had received postoperative radiotherapy. Her flap healed without necrosis. Data of nine patients were included in the final evaluation.

The preoperative plasma ET-1 concentrations were 8.9 (5.5–12.5) pg/ml (median, 25–75 quartiles). At one and three hours after induction of anesthesia (phases 2 and 3) and at the end of operation (phase 4), they were significantly lower, near 3 pg/ml on average. Ten minutes after the patients' arrival in the recovery room, plasma ET-1 concentrations were significantly higher than at the end of opera-

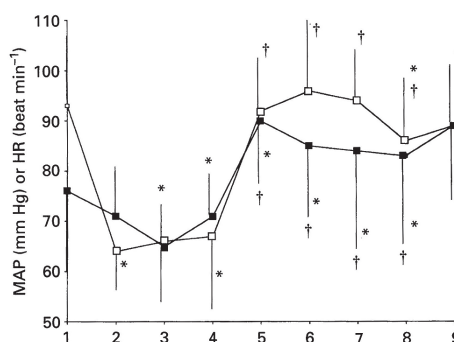


Figure 15. Perioperative changes in mean arterial pressure (MAP, white squares) and heart rate (HR, black squares). Values are given as mean \pm SD. * represents $p < 0.05$ compared with values measured before induction and † $p < 0.05$ compared with values at the end of the operation. Measurement times as in Table VIII.

tion, but did not differ significantly from the concentrations before induction. They stayed around 5 pg/ml until the end of the study.

Peripheral vasoconstriction

T_{grad} of 3.9 (3.4–4.5) °C indicating vasoconstriction was observed preoperatively. During the operation, T_{grad} was negative, indicating vasodilation. After the operation, vasoconstriction developed again, T_{grad} being at its highest one and two hours after the patients arrived in the recovery room (phases 7 and 8). Thereafter, peripheral cutaneous vasoconstriction diminished, but some vasoconstriction was still observed at the end of the study (Figure 14).

Blood pressure and heart rate

During anesthesia, MAP was significantly lower than before induction. Postoperatively, it differed from the pre-induction level only at two hours after arrival in the recovery room. All MAP values measured in the recovery room were significantly higher than those measured at the end of the operation. HR remained at the pre-induction level during the operation. At all measurement times in the recovery room, it was significantly higher than the level before induction and also the level at the end of the operation (Figure 15).

Healing of flaps

Four of the nine TRAM flaps healed uneventfully. There was minor skin necrosis in three flaps and fat necrosis in two flaps. The three flaps with skin necrosis needed surgical revision. The final result in all flaps was satisfactory.

Correlation of ET-1 with measured parameters

In the nonparametric Spearman rank correlation test, a statistically significant nonlinear correlation existed between ET-1 and T_{grad} ($r = 0.32$, $p < 0.01$) and between ET-1 and MAP ($r = 0.25$, $p < 0.05$), but not between ET-1 and HR. A statistically significant nonlinear correlation was present between the preoperative T_{grad} and development of necrosis ($r = 0.81$, $p < 0.01$). No statistically significant correlation was found between development of necrosis and intra- and postoperative T_{grad} values or ET-1 levels.

5.4. Effect of felodipine on plasma ET-1 concentrations, peripheral vasoconstriction, postoperative $P_{\text{tc}} O_2$, and survival of free TRAM flaps (IV)

The characteristics of the patients and operations were comparable within the groups. In the control group, one patient developed a postoperative hematoma necessitating surgical evacuation, one patient suffered from pneumonia, and one patient had a postoperative pulmonary embolism.

Plasma ET-1 concentrations

The preoperative plasma ET-1 concentrations were 6.1 (4.6–7.7) pg/ml (means, 95 % CIs) in the felodipine group and 7.3 (5.3–9.3) pg/ml in the control group. No statistically significant differences were present in ET-1 concentrations between the study groups at any measurement time (Figure 16).

Temperature

Before induction of anesthesia, T_{grad} was 2.3 (0.5–4.0) °C in the felodipine group and 2.4 (0.3–4.5) °C in the control group. There were no statistically significant differences in T_{grad} between the study groups during the study period (Figure 17). In both groups, T_{rect} decreased during the first hour of anesthesia and was at its lowest three hours after induction,

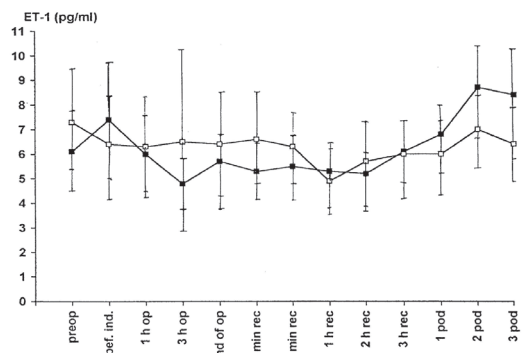


Figure 16. Perioperative changes in plasma ET-1 levels in the felodipine and control groups. Values are given as means (95 % CIs). The black squares represent the felodipine group and white squares the control group.

35.8 (35.2–36.3) °C in the felodipine group and 35.9 (35.6–36.2) °C in the control group. It increased again in the recovery room, peaking three hours after the operation to 37.3 (36.8–37.8) °C in the felodipine group and 37.4 (37.0–37.8) °C in the control group. No statistically significant differences were observed in T_{rect} between the two study groups at any measurement time.

Blood pressure and heart rate

Throughout the study period, HR was higher in the felodipine group than in the control group. The difference was statistically significant before induction [90.6 (81.3–99.9) beats per min (bpm) in the felodipine group and 76.2 (67.0–85.4) bpm in the control group, difference of means 14.4 (2.2–26.6), $p < 0.05$] and 10 minutes after arrival to the recovery room [88.8 (78.6–99.0) in the felodipine group and 75.1 (65.6–84.6) in the control group, difference of means 13.7 (0.7–26.7), $p < 0.05$].

The preoperative MAP was 92.5 (83.6–101.4) mmHg in the felodipine group and 89.4 (81.5–97.3) mmHg in the control group. Throughout the study period, no statistically significant differences in MAP were observed between the groups.

Healing of flaps

The ipsilateral and contralateral $P_{\text{tc}}O_2$ decreased in both groups from the initial 50 mmHg to a lower level during the postoperative period. The felodipine and control groups

did not differ statistically with regard to $P_{\text{tc}}O_2$ at any measurement time. In both groups, two of ten patients developed a minor cutaneous necrosis of the contralateral flap edge, which healed without surgical revision. In these patients, the contralateral $P_{\text{tc}}O_2$ was near zero in the recovery room and during the first days on the ward. In the felodipine group, a statistically significant difference was present in the contralateral $P_{\text{tc}}O_2$ between the patients with and without necrosis in the recovery room ($p < 0.05$).

5.5. Effect of indices of obesity on cutaneous or fat necrosis in pedicled TRAM flaps (V)

Six of the 12 patients had ideal relative body weight (BMI 19–24), one was slightly underweight (BMI <19), three were slightly overweight (BMI 25–27), and two were moderately overweight (BMI 28–30). No patients in this study were obese (BMI >30). At the time of the study, marked obesity was considered a contraindication for TRAM flap breast reconstruction in Helsinki University Central Hospital. Based on WHCR, four patients had an upper type, two a medium type, and six a lower type body fat distribution.

Thickness of the subcutaneous fat on the ipsilateral side of the pedicled TRAM flap was preoperatively 23.2 mm (mean) (range 12.5–37.3). One week after the operation, it had increased significantly to 33.4 mm (19–44.8) ($p < 0.01$ compared with the preoperative level), remaining at this level for the remainder of the study period.

Of the 12 patients, four developed minor cutaneous necrosis on the edge of the contralateral side of the TRAM flap and one developed fat necrosis seen on ultrasonography. Three of the patients with cutaneous necrosis needed surgical revision. There were no significant differences in fat thickness between the patients with and without cutaneous or fat necrosis at any measurement time.

No statistically significant differences were present in development of necrosis between the groups based on BMI. Necrosis was more com-

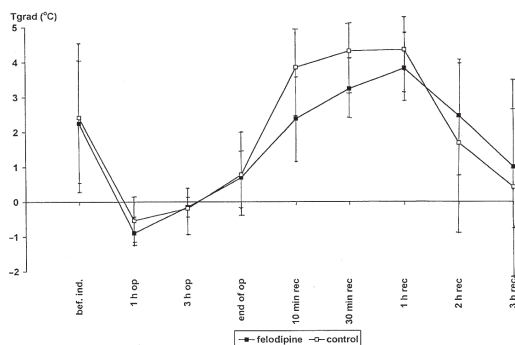


Figure 17. The perioperative changes in T_{grad} in the felodipine and control groups. Values are given as means (95 % CIs).

mon in patients with a WHCR of less than 0.80, i. e. in patients with a lower body type body fat distribution (four of six developed necrosis), than in patients with an upper or medium body

type fat distribution. In patients with a WHCR of more than 0.84, there were no cases of necrosis. These differences were not, however, statistically significant (Table X a and b).

Table X. Presence of cutaneous or fat necrosis in patients grouped (A) by body mass index (BMI) and (B) by waits-hip circumference ratio (WHCR).

A			B		
BMI (kg/m²)	Necrosis (n = 5)	No necrosis (n=7)	WHCR	Necrosis (n = 5)	No necrosis (n = 7)
<19	0	1	< 0,80	4	2
19-24	3	3	0,80-0,84	1	1
25-27	2	1	>0,84	0	4
28-30	0	2			

6 Discussion

6.1. Perioperative changes of cutaneous blood flow in TRAM flaps (I, II)

Breast reconstruction with the TRAM flap is performed on tens of thousands of women worldwide each year. The fairly common disturbances in the flap's cutaneous blood flow may lengthen the treatment, increase costs, and sometimes spoil the result of the operation. Before the studies presented in this thesis, the behavior of the cutaneous blood flow in different phases of the TRAM flap operation was unknown.

The temperature of the patient can affect cutaneous blood flow (Rowell 1974, Boulant 2000, Kellogg 2006). Temperature and flap blood flow are also connected to each other. In an experimental study on dogs, flap blood flow varied directly with temperature (Awwad 1983). Moreover, hypothermia decreased blood flow in the rat epigastric flap (Kinnunen 2002). The changes measured in cutaneous blood flow in the studies of this thesis can be assumed not to have resulted from changes in the patient's temperature, because during these studies the patients remained fairly normothermic due to the high ambient temperature (24 °C), the use of a warming mattress, and warmed infusion fluids.

Anesthesia affects mainly cutaneous, not the subcutaneous blood flow in humans (Saumet 1988). All inhaled anesthetics induce vasodilation in the skin (Ozaki 1995, Ozaki 1997). The vasodilatory effect of isoflurane is more potent than that of halothane (Mulholland 1994). In the present studies, the patients were anesthetized with isoflurane. The decrease in LDF level after ligation of DIEA was likely not caused by the anesthesia itself. It has been observed experimentally that blood flow measured by LDF is maintained well during normovolemic conditions in musculocutaneous flaps both with halothane and isoflurane anesthesia (Sig-

urdsson 1994). Our patients were kept mildly hypervolemic and hemodiluted in all studies, as recommended for microvascular surgery (Robins 1983, Macdonald 1985, Sigurdsson 1995).

6.1.1. *Pedicled TRAM flaps (I)*

The results of Study I show that the elevation of the contralateral side of the pedicled TRAM flap caused an increase in cutaneous blood flow, more clearly on the ipsilateral side of the flap. Before the operation, blood supply to the skin and subcutis of the TRAM flap area originated from the DIEA, whose branches run as paraumbilical and infraumbilical perforators through the rectus muscles to the vascular plexuses near the surface of the skin (Boyd 1984, Moon 1988). When the contralateral side of the TRAM flap is elevated, the perforators rising from the underlying rectus muscle are ligated, and the natural route for cutaneous blood flow is lost. One would expect then a decrease in the cutaneous blood flow because after its elevation the contralateral skin and subcutis island receive blood only indirectly from the ipsilateral side through anastomotic channels in the subdermal plexus (Taylor 1984) and distinct subcutaneous periumbilical arteries (Kaufman 1985). However, in this study, hyperemia was observed with LDF when the contralateral part of the flap was elevated in pedicled TRAM flaps. The significant increase in LDF level on the ipsilateral side could be caused by opening up of the choke vessels between adjacent vascular angiosomes, leading to increased blood flow from the SEA system (Taylor 1987). Opening of the arteriovenous shunts has been found after elevation of a myocutaneous rectus abdominis island flap in pigs (Hjortdal 1991). Our findings suggest that the same phenomenon may occur in humans.

Some degree of hyperemia was also measured on the contralateral side of the flap. This might be the result of opening up of the para- and infraumbilical reduced-caliber choke vessels (Taylor 1984). The opening of the choke vessel may be stimulated by hypoxia caused by elevation of the contralateral side.

A similar hyperemia was observed after elevation of musculocutaneous flaps in dogs by Gottrup and coworkers (Gottrup 1984). Boyd and colleagues observed in a controlled experimental study that a delay procedure, preoperative ligation of SEA in TRAM flaps, resulted in a postoperative increase in the amount of viable flap skin. The authors speculated that transient hypoxia resulting from ligation of SEA may play a role in triggering DIEA to take over some of the territory previously perfused by SEA (Boyd 1990). Later, the delay procedure was found to lead to dilation of the choke vessels between adjacent territories and not to ingrowth of new vessels (Dhar 1999). Ribuffo and coworkers used the study setting and protocol originally presented in Study I and measured blood flow with LDF and echo color-flow in pedicled TRAM flaps. They confirmed our results, showing hyperemia when the contralateral side of the pedicled TRAM flap is elevated (Ribuffo 1997).

In Study I, ligation of the DIEA caused a significant decrease in LDF value on the contralateral side. Skin blood flow on the contralateral side of the flap did not return to the baseline until the first postoperative day. The ipsilateral cutaneous blood flow remained near the baseline level at all postoperative measuring times. Based on these results, the SEA apparently cannot provide adequate perfusion to the contralateral skin paddle immediately after ligation of the DIEA, which is the dominant artery of the TRAM flap (Boyd 1984, Hendricks 1994). The return of LDF levels to the baseline on the postoperative days could be speculated to be a sign of SEA being able to increase blood flow in the flap gradually after the operation by keeping the choke vessels open. The origin of microvascular blood flow, previously from DIEA, must be reversed if the whole flap is to survive after the operation.

Soon after Study I Harris and coworkers

published their report. They demonstrated in an intraoperative investigation of 17 pedicled TRAM flaps that occlusion of the SEA at the upper level of the skin flap caused a decrease in DIEA blood flow measured by ultrasound. They assumed that survival of all lower TRAM flap tissues requires reversal of the direction of blood flow to the flap (Harris 1992), in accordance with our opinion.

In this study, the contralateral $P_{tc}O_2$ fell to a very low level after the whole flap was elevated and the DIEA was ligated. It remained near zero until the seventh postoperative day, when the measurements ceased. Very low $P_{tc}O_2$ values have been found in surviving flaps postoperatively (Achauer 1980, Svedman 1982, Gottrup 1984). In 1983, Raskin and his group and later Hjortdal and coworkers concluded that low $P_{tc}O_2$ levels measured after elevation of island flaps were caused by decreased blood flow in the subdermal plexus. They speculated that sympathetic denervation would stimulate opening up of the arteriovenous shunts and a decrease in blood flow in the most superficial cutaneous layers (Raskin 1983b, Hjortdal 1991). This could explain the very low $P_{tc}O_2$ values measured after DIEA ligation and during the postoperative period in Study I. $P_{tc}O_2$ has been postulated to reflect oxygen delivery and consumption in the skin, and low oxygen tension may be an indirect measure of increased metabolic rate in the skin (Achauer 1984). Low postoperative $P_{tc}O_2$ levels in these patients might also be a sign of increased consumption of oxygen. The slow increase in $P_{tc}O_2$ during the postoperative week could indicate that a few days after the operation SEA is gradually able to maintain blood flow also in the most superficial cutaneous layers.

The postoperative $P_{tc}O_2$ levels were constantly lower on the contralateral side of the flap than on the ipsilateral side. This is probably caused for anatomical reasons, as the contralateral side is postoperatively less perfused than the ipsilateral side due to cutting of the perforators during flap elevation.

After this work, other studies have been conducted on the hemodynamics of pedicled TRAM flaps. Codner and colleagues measured intravascular blood pressure of DIEA and the

corresponding vein before and after bipediced TRAM flap breast reconstructions in patients with and without delay. They observed an increase in DIEA and vein blood pressure after transfer of the flap to the chest, indicating an increase in flap blood flow. Postoperatively, they observed a decrease in TRAM flap perfusion pressure in flaps without delay and an increase in flaps with delay (Codner 1994). Ribuffo and coworkers noted a similar decrease as in the present study in the contralateral LDF level of pedicled TRAM flaps when the DIEA was ligated. They also thought that this is due to blood flow inversion (Ribuffo 1997). In the studies of Clugston and coworkers, DIEA and the concomitant vein were cannulated. Their measurements showed that the venous pressure increased and the perfusion pressure decreased when the flap was rotated to the chest (Clugston 1998). However, unlike in our study, they did not measure cutaneous blood flow.

Scheufler et al have demonstrated by angiography the opening of choke arteries between the superior and the deep inferior epigastric systems (Scheufler 2000). In another recent study of 11 pedicled TRAM flaps Scheufler and associates found an increase in the systolic peak flow of the SEA early after surgery. Consistent with our view, they speculated that hypoxia in the flap tissue could lead to opening of choke arteries between the superior and deep inferior epigastric arteries (Scheufler 2004).

6.1.2. Free TRAM flaps (II)

Cutaneous blood flow between pedicled and free TRAM flaps was not compared in the same study. However, some conclusions between the pedicled flaps in Study I and the free flaps in Study II can be drawn, because the patients, operating conditions, anesthesia, and measurements were similar.

On an anatomical basis, one might expect that cutaneous blood flow would be better in free than in pedicled TRAM flaps since the free flap is supplied by the dominant pedicle of the TRAM flap, the DIEA (Boyd 1984, Hendricks 1994), and the pedicled flap by the nondominant pedicle, the SEA. The results of Studies I

and II confirm the clinical observations of the free TRAM flap demonstrating very few circulatory complications. In Study II, only one of 11 patients developed a minor skin necrosis and one a fat necrosis, compared with Study I, where eight of 14 pedicled TRAM flaps showed signs of minor cutaneous necrosis. The more reliable cutaneous blood flow in free flaps has not been demonstrated with hemodynamic measurements earlier in the literature. Nowadays the majority of TRAM flap breast reconstructions are performed in Finland with a free TRAM flap and newer modifications such as the DIEP or SIEA flap. Pedicled TRAM flaps are used in selected cases, especially outside microsurgical units.

In free TRAM flaps, the ipsilateral and contralateral LDF values increased, as in pedicled flaps in Study I, during the elevation of the contralateral flap island and decreased to or below the initial level when the whole flap was elevated and the rectus muscle cut. Because the elevation procedures are rather similar in pedicled and free flaps, no differences were expected.

When the DIEA and vein were cut and the free flaps were positioned on the chest, a significant decrease in the contralateral $P_{tc}O_2$ and LDF levels was observed in free flaps as a sign of reduction of blood flow. The LDF levels in the free flaps did not decrease to zero, although the flap was without blood flow. LDF is unable to distinguish between nutrient and non-nutrient blood flow, and thus LDF seems to misinterpret the non-nutrient random movement of cells in a nonperfused tissue as blood flow (Marks 1984).

In the recovery room, when the anastomoses were functioning, ipsilateral and contralateral LDF levels returned to baseline levels in the free flaps. This result differs from the pedicled flaps, where the contralateral LDF levels in the recovery room were still significantly lower than at the beginning of the operation. In the recovery room, the contralateral $P_{tc}O_2$ was low compared with the initial level in free flaps, but had increased markedly compared with the values measured before the anastomoses were formed. The ipsilateral $P_{tc}O_2$ had increased to the preoperative level in the recovery room,

and on the third postoperative day it was near the initial level on both sides of the free flaps. These findings differ clearly from the pedicled TRAM flaps (Study I) where the $P_{tc}O_2$ levels were very low throughout the postoperative period. The SEA apparently cannot perfuse the pedicled flap adequately on the first days after the operation. These results indicate that the postoperative blood flow in the free TRAM flap, measured by $P_{tc}O_2$ and LDF is more generous than in the pedicled flap. This phenomenon likely results mainly from the free flap being supplied by the dominant pedicle of the TRAM flap, the DIEA, while the nondominant pedicle SEA supplies the blood flow of the pedicled TRAM flap.

The contralateral LDF and $P_{tc}O_2$ levels were constantly lower than the ipsilateral values at each measuring time in pedicled as well as in free TRAM flaps. This result agrees with the anatomical findings suggesting that the ipsilateral cutaneous perfusion is superior to the contralateral blood flow (Dinner 1983, Moon 1988). The LDF and $P_{tc}O_2$ were measured at zones I and III; these zones are numbered according to the original classification of skin zones of the TRAM flap, where perfusion is best in zone I and worst in zone IV (Hartrampf 1982, Schefflan 1983a and 1983b). Hallock has later investigated cutaneous blood flow intraoperatively in free TRAM flaps with LDF (Hallock 2001). They confirmed the findings of the present studies, showing that LDF levels were at all times higher on the ipsilateral than on the contralateral side of the TRAM flap skin. They also revealed that the DIEA is the dominant source vessel of the TRAM flap compared with the SEA, as has been assumed based on anatomical studies (Boyd 1984, Hendricks 1994). Hallock and coworkers stated that a relative ischemia exists contralaterally even in free TRAM flaps (Hallock 2001).

6.2. Prediction of cutaneous necrosis in pedicled TRAM flaps (I)

According to clinical studies, cutaneous necrosis is more common in pedicled than free TRAM flaps, which is why the free TRAM flap has

gradually exceeded the pedicled TRAM flap in popularity as a breast reconstruction method, despite the procedure being more demanding. Breast reconstruction with a pedicled TRAM flap can be performed with less microsurgical experience. If the pedicled TRAM flaps prone to cutaneous necrosis could be identified during or immediately after surgery, some surgical or pharmacological interventions could be attempted to enhance blood flow in the flap, and thus to increase the success rate.

In Study I, cutaneous necrosis was observed during the study period on the contralateral side of eight of the 14 the pedicled TRAM flaps (57 %), which is comparable with the incidence rates given in the literature (Hartrampf 1987, Schusterman 1992, Elliott 1993, Kroll 1998, Paige 1998, Clugston 2000, Garvey 2006). Factors known to increase the risk of cutaneous necrosis in pedicled TRAM flaps are smoking (Chang 2000a, Padubidri 2001, Selber 2006, Booi 2007) and obesity (Berrino 1991, Moran 2001, Ducic 2005, Spear 2007). However, in Study I, only one patient smoked and her flap healed without complications. The weight of the patients did not differ between the patients with and without cutaneous necrosis of the flap.

Based on the results of Study I, intraoperative LDF measurements appear to be able to predict cutaneous necrosis of the pedicled TRAM flap. The contralateral LDF value after ligation of the DIEA decreased more in flaps developing cutaneous necrosis than in flaps healing uneventfully. The difference between the flaps with and without necrosis remained significant until the first postoperative day.

The contralateral LDF level decreased after ligation of the DIEA to 43 ± 7 % of the initial value in the flaps developing cutaneous necrosis. Based on this finding, the pedicled TRAM flaps prone to cutaneous necrosis can be identified with intraoperative LDF measurements. It is important to be able to identify the flaps susceptible to cutaneous necrosis during the operation because the surgical plan can still be changed from the pedicled flap to one with a more secure blood flow.

Later, in a retrospective study of 94 free flaps, postoperative LDF identified developing

complications before they were clinically visible. If LDF level decreased to less than 50 % of the baseline for 30 minutes or longer, aggressive exploration was considered necessary (Heller 2001). In a recent study of muscle-sparing free TRAM flaps, a lower blood flow was observed with LDF in zone IV of patients with flap complications compared with patients without flap complications (Booi 2008). Their results are in accordance with ours.

$P_{tc}O_2$ levels were significantly lower in flaps developing necrosis than in flaps without necrosis contralaterally on the third and seventh postoperative days and ipsilaterally at all postoperative measuring times. Development of necrosis could not, however, be predicted based on the intraoperative $P_{tc}O_2$ values.

An oxygen challenge test, a response of $P_{tc}O_2$ to increased inspired oxygen concentration, has been claimed to be a sign of intact circulation and flap survival (Achauer 1980). In the present study, a negative oxygen test was observed in the two patients with the broadest (50 mm) necrotic areas. In the other six patients with smaller necrotic areas, the oxygen test gave contradictory results. A possible explanation for this is that the $P_{tc}O_2$ probes were not exactly over the contralateral edge (zone IV), where the necrosis developed, but were placed a little more centrally in the flap.

If the flaps at risk of developing cutaneous necrosis could be identified intraoperatively with LDF, $P_{tc}O_2$, or other monitoring methods, some approaches augmenting flap blood flow could be tried during the same operation. A new promising monitoring method is intraoperative ICG fluorescence video angiography, which has been used to visualize the individual perfusion map in pedicled TRAM flaps. It might be useful for showing the area that should be discarded because of poor perfusion (Yamaguchi 2004). One attempt to improve flap blood flow has been to add a microsurgical anastomosis to a pedicled TRAM flap (Harashina 1987, Schefflan 1988). In Study II, we measured skin blood flow in four pedicled TRAM flaps with an additional microvascular anastomosis in the axilla. In these four patients, the postoperative $P_{tc}O_2$ and LDF levels were higher than the levels in the pedicled flaps in Study I, but

lower than in the free flaps of Study II. The number of patients is too low for drawing any conclusions. Various pharmacological agents, such as VEGF and endothelin antagonists (Tane 1995, Inoue 1998, Erni 2005, Wettstein 2007) have been applied to enhance flap blood flow, but usually these must be administered before the operation. An ideal agent could be administered to the patient at the moment that the risk for decreased flap flow is observed. Nitric oxide precursors administered during the operation have yielded promising results in preventing ischemia-reperfusion injury in myocutaneous flaps of pigs (Cordeiro 1998).

6.3. Relation of plasma ET-1 concentrations to peripheral vasoconstriction, blood pressure, heart rate, and cutaneous or fat necrosis (III)

A long-lasting vasoconstriction is common during and after prolonged operations such as reconstructive procedures. Cutaneous vasoconstriction is known to depend on body temperature (Rowell 1974, Boulant 2000, Kellogg 2006). The role of ET-1, a powerful vasoconstrictory peptide secreted from endothelial cells, in development of intra- and postoperative vasoconstriction remains obscure. In experimental studies, administration of ET-1 has reduced blood flow in skin flaps (Samuelson 1992, Inoue 1998) and decreased flap survival (Tane 1995).

A relationship between plasma ET-1 concentrations and peripheral vasoconstriction was observed in this study. The increase of plasma ET-1 levels and T_{grad} coincided preoperatively and postoperatively. Elevated plasma ET-1 concentrations have been measured during severe hemodynamic stress, myocardial ischemia, sepsis, and trauma (Cernacek 1989, Koller 1991, Pittet 1991). Elevated ET-1 levels have also been observed during surgery (Hirata 1989). In Study III, slightly elevated plasma ET-1 levels were measured preoperatively and postoperatively. The highest values were noted before induction. The cause for the

increased preoperative ET-1 levels is unclear. ET-1 is known to be released as a result of hypoxia, stretch, increased intramural pressure, and cold (Gandhi 1994). Systemic hypoxia can be assumed not to be the cause for elevated ET-1 levels in Study III. Before induction, the patients' peripheral oxygen saturation was normal, and the intra- and postoperative PaO₂ levels were also within normal limits. A T_{grad} of 3.9 °C, indicating peripheral vasoconstriction, was observed preoperatively. Possibly, adrenergic stimulation following anxiety, despite benzodiazepine premedication, resulted in peripheral vasoconstriction, which could have induced peripheral hypoxia and hypothermia, leading to ET-1 release. The increase in the preoperative plasma ET-1 concentration could also have arisen from the pain due to insertion of the antecubital venous cannula, since local anesthesia was not used for the cannulation. Whether minor pain causes changes in ET-1 levels, is unknown.

During the operation the ET-1 levels were within normal limits in Study III, around 3 pg/ml. In the study of Shirakami and coworkers plasma ET-1 levels remained near preoperative values during minor surgery, including total knee replacement, cholecystectomy, or hysterectomy. During major operations, such as gastrectomy, esophagectomy, hepatectomy or heart surgery, ET-1 levels were higher than before the operation (Shirakami 1995). In Study III, the breast reconstruction with a pedicled TRAM flap could be assumed to be comparable with the minor surgical procedures in which the ET-1 levels were not elevated in Shirakami's study.

Peripheral vasoconstriction was not observed one hour after the induction of anesthesia. On the contrary, T_{grad} was reduced, indicating vasodilation, which lasted throughout the operation. The vasoconstrictive effect of the high pre-induction level of plasma ET-1 on the microvessels may have been prevented with the use of isoflurane during anesthesia. Like all inhaled anesthetics, isoflurane inhibits central thermoregulatory control (Ozaki 1997, Ozaki 1995). The vasodilatory effect of isoflurane is mediated by stimulating the β -adrenergic receptors of vascular smooth muscle (Philbin

1995), but probably not by releasing nitric oxide (Brendel 1992, Johns 1993). The isoflurane-induced vasodilation may have exceeded the vasoconstrictory effect of ET-1 during anesthesia. Moreover, if the initial ET-1 release was transient, it could have caused vasodilation by stimulating nitric oxide or prostacyclin release (Johns 1993).

Postoperatively, an increase in the plasma ET-1 concentrations was measured ten minutes after arrival in the recovery room. The ET-1 levels in the recovery room remained slightly elevated, around 5 pg/ml, compared with the intraoperative levels. Elevated plasma ET-1 levels have been measured during the first postoperative hours in several studies (Itoh 1991, Miyaguchi 1991, Sato 1992). In another study, increased ET-1 levels were observed postoperatively in patients receiving a knee arthroplasty. The maximal plasma ET-1 concentration was measured 1.5 hours after the end of surgery, when ET-1 concentrations were 2.9 times the preoperative value (Matziolis 2005). In a study of elderly patients undergoing major surgical procedures, the plasma ET-1 concentrations were elevated preoperatively and postoperatively in patients with hypertension compared with patients with normal blood pressure (Nelson 1999). ET-1 was not measured intraoperatively in that study.

An increase in T_{grad} as a sign of vasoconstriction was measured as soon as the patients were transferred to the recovery room. The vasoconstriction disappeared by the end of the recovery room period. At the same time, plasma ET-1 concentrations were higher than during the operation. The postoperatively elevated plasma ET-1 concentrations appear to be associated with peripheral hypothermia. The peripheral vasoconstriction manifesting during the immediate postoperative hours may cause release of ET-1 from the peripheral parts of the body. Alternatively, surgical stress and manipulation of tissues have been suggested to induce increased ET-1 release after operations (Onizuka 1992, Onizuka 1993, Shirakami 1993) and may have caused the peripheral vasoconstriction.

A statistically significant correlation existed between plasma ET-1 concentrations

and MAP. The elevated ET-1 values pre- and postoperatively were accompanied by rather high MAP levels. This result is in accordance with earlier findings showing that ET-1-induced vasoconstriction leads to an increase in blood pressure but does not affect heart rate (Remuzzi 1993, Gandhi 1994). Elevated ET-1 levels have been measured in several disease states with disturbed vascular control, e.g. Raynaud's phenomenon, pulmonary hypertension, and subarachnoid hemorrhage (Miller 1993, Remuzzi 1993, Gandhi 1994). There may be several mechanisms underlying development of high blood pressure pre- and postoperatively, and endothelin may be one of them. ET-1 antagonists are in clinical use in the treatment of pulmonary hypertension and in phase III testing for the treatment of vasospasm after subarachnoid hemorrhage.

In this study, no statistical connection between ET-1 concentrations and development of cutaneous necrosis was found. Flap blood flow was not measured in Study III, but the development of necrosis was observed clinically. One of the many factors causing cutaneous necrosis is intense vasoconstriction of the flap vessels, leading to decreased flap microcirculation (Khouri 1992). ET-1 may be an important regulator of the flap blood flow, affecting the development of necrosis (Menger 1992, Samuelson 1992, Tane 1995, Inoue 1998, Pang 1998, Mobley 2003). Studies on the effect of ET antagonists on flap blood flow and development of necrosis have recently yielded promising results (Tane 1995, Inoue 1998, Erni 2005, Wetstein 2007). In our study, the small size of the patient group may have masked the connection between ET-1 and cutaneous necrosis. Future studies are needed to determine the relation of ET-1, cutaneous blood flow, and development of necrosis in surgical flaps.

The blood samples for plasma ET-1 determinations were drawn from the limb on which T_{ind} and T_{ant} probes were positioned. The elevated ET-1 levels observed before induction could be assumed to reflect a considerable local release of ET-1 from the same limb. ET-1 is a local hormone. Most of its release from the vascular endothelium is directed to the muscle layer of the vessel and not to the bloodstream.

Circulating ET-1 levels are thought to greatly underestimate local concentrations (Wagner 1992). The circulating half-life of ET-1 is only 3.5 minutes (Vierhapper 1990). Very small intravenous doses of synthetic ET-1 cause an increase in forearm blood flow in humans. When the ET-1 dose increases, blood flow decreases as a result of an intense vasoconstriction of the small arteries and arterioles with a duration of at least two hours (Remuzzi 1993, Gandhi 1994). Vasoconstriction develops slowly, in 15–20 minutes, in segments of human mesenteric arteries (Miyauchi 1990). Fast pulmonary clearance for ET-1 has been observed in some animal models, but this has been questioned in humans (Gandhi 1994).

The cause for the high ET-1 levels of the patient who was excluded remains obscure. Incorrectly high ET-1 values can be seen after incomplete lyophilization, which is unlikely in this case, since dozens of samples were handled simultaneously in the radioimmunoassay. Hemoglobin remaining in the sample may also lead to very high ET-1 values; however the method used of extraction removes all hemoglobin from the sample.

6.4. Effect of felodipine on plasma ET-1 concentrations, peripheral vasoconstriction, postoperative $P_{tc}O_2$, and survival of free TRAM flaps (IV)

Administration of calcium antagonists has suppressed ET-1 release and subsequent vasoconstriction in experimental and clinical studies (Kiowski 1991, Liu 1994, Kobayashi 2001, Yakubu 2002). Calcium antagonists have also reduced the incidence of necrosis of flaps in some experimental studies (Hira 1990, Pal 1991, Yessenow 1991, Baillet 1994), while having no effect in others (Miller 1985, Emery 1990). Felodipine is a vasodilatory dihydropyridine calcium antagonist capable of relaxing arterial resistance vessels (Ljung 1985). Theoretically, it might be able to decrease perioperative ET-1 levels and vasoconstriction and increase cutaneous blood flow in a flap. However, felodipine

had no effect on plasma ET-1 concentrations, T_{grad} , or postoperative $P_{\text{tc}} O_2$ of free TRAM flaps in this prospective, double-blind, and randomized study (IV).

In Study IV, the plasma ET-1 levels on the preoperative and postoperative days were quite high compared with levels in healthy humans at rest (0.5–5 pg/ml) (Karwatowska-Prokopczuk 1990). Elevated ET-1 levels have been measured during major operations, e.g. heart surgery or gastrectomy (Shirakami 1995). Endothelin may play a role in the no-reflow phenomenon seen in free flaps and replanted digits (Lantieri 2003). Breast reconstruction with a free TRAM flap is a time-consuming operation with a fairly long ischemia in the flap and extensive manipulation of vessels during the preparation and performing of anastomoses. Stretch and ischemia are among factors increasing ET-1 release (Gandhi 1994). The stretch and manipulation of the recipient and flap vessels and ischemia of the flap before the anastomoses are completed might have induced marked local ET-1 release, seen as relatively high plasma ET-1 concentrations in Study IV.

In Study IV, the intraoperative and postoperative ET-1 concentrations were determined from arterial plasma. However, venous plasma ET-1 concentrations reflect the actual levels in the tissues more accurately than arterial concentrations since ET-1 is released locally (Wagner 1992) and the pulmonary clearance of ET-1 from plasma is very rapid (Gandhi 1994). The venous ET-1 concentrations have been found to be higher than arterial concentrations in healthy humans (Wagner 1990). The arterial ET-1 concentrations were measured in Study IV on the operation day because the aim was to determine out the ET-1 level in the blood flowing to the flap. An effect of felodipine on ET-1 concentrations might have been observed, if the ET-1 levels had been measured from the vein of the flap pedicle. Venous ET-1 concentrations would have given a clearer image of the actual amount of ET-1 release in the flap. Recently, Lantieri and coworkers measured ET-1 concentrations from peripheral venous plasma and the venous blood running from the flap in 20 patients during breast reconstructions with free TRAM or DIEP flaps. They observed an

increase in ET-1 concentration in the venous blood from the flap, but not in peripheral venous blood, after opening of the arterial anastomosis. They speculated that increased ET-1 level could be an explanation for the vasospasm seen in free flaps (Lantieri 2003).

T_{grad} has been shown to correlate well with volume plethysmography as a sign of peripheral blood flow (Rubinstein 1990). The degree of vasodilation judged by T_{grad} was similar in the two study groups, although T_{grad} tended to be lower in the felodipine group during the first hour after the operation. A larger dose of felodipine possibly could have had a clearer vasodilatory effect. The dosage of oral felodipine, 5 mg at 22:00 hours and 5 mg eight hours later, was chosen based on the daily doses used for treatment of hypertension (2.5–10 mg once daily). In unanesthetized healthy subjects, 15 mg of felodipine causes an increase in forearm blood flow and a decrease in forearm peripheral resistance (Agner 1985). However, a dose of felodipine larger than the one used to treat of hypertension increases the risk of excessive tachycardia and hypotension. Despite its powerful vasodilatory capacity, felodipine may be no more effective than other calcium antagonists in preventing vasoconstriction under clinical circumstances resembling the ones of this study.

The given dose of felodipine was clinically effective based on the pre-induction HR, which was significantly higher in the felodipine group than in the control group. Felodipine, with its vasodilating properties, caused a decrease in systemic vascular resistance in this study, based on the increase of HR and no changes in MAP. Felodipine had no effect on the pre-induction or on intraoperative MAP values. In healthy subjects, a single dose of felodipine increases resting HR (Agner 1985, Carruthers 1987). In this study, HR during and after anesthesia stayed at a higher level in the felodipine group than in control patients, showing that the effect of felodipine continued up to the postoperative period. The highest MAP levels in both groups were measured 30 minutes and one hour after the patients had arrived in the recovery room. In healthy subjects, felodipine has no effect or only causes a minor decrease in mean resting blood pressure (Agner 1985, Carruthers 1987).

The postoperative rise of blood pressure is part of the stress response induced by surgery (Halter 1977). According to this study, felodipine has a minor decreasing effect on postoperative blood pressure, probably because of its vasodilatory capacity.

Felodipine and control groups did not differ with regard to $P_{tc}O_2$ values or development of necrosis of the flap. This is in contrast to some experimental studies, where the incidence of necrosis was reduced by calcium antagonists (Hira 1990, Pal 1991, Yessenow 1991, Bailet 1994). In both groups of Study IV, two of the ten patients developed a minor cutaneous necrosis on the contralateral side of the flap. This is consistent with the incidence of cutaneous necrosis reported in studies on free TRAM flaps (Schusterman 1994, Trabulsky 1994, Chang 2000, Kroll 2000, Nahabedian 2002b). The incidence of cutaneous necrosis is much higher in pedicled than free TRAM flaps (Harttrampf 1987, Schusterman 1992, Elliott 1993, Kroll 1998, Paige 1998, Clugston 2000, Garvey 2006). The effect of felodipine might have been clearer had the study groups consisted of patients with pedicled instead of free TRAM flaps.

6.5. Effect of indices of obesity on cutaneous or fat necrosis in pedicled TRAM flaps (V)

Cutaneous necrosis is a common complication in pedicled TRAM flaps. It usually develops in the most distal contralateral part of the flap (zone IV). Surgical revisions are often needed to treat the necrotic area. They increase costs, lengthen hospital stay, and cause physical and emotional distress to the patient. Overweight and obesity increase the risk of cutaneous necrosis in pedicled TRAM flaps according to several studies (Berrino 1991, Moran 2001, Ducic 2005, Spear 2007), but one earlier study reported that obesity had no effect on incidence of cutaneous necrosis (Kroll 1989). Fat necrosis has been observed in pedicled flaps of obese patients more often than in patients with ideal weight (Berrino 1991). Obesity has been determined in those studies as $BMI \geq 30$ (kg/

m²). Based on our results, BMI and cutaneous or fat necrosis do not seem to be associated. The small size of the patient group is, however, a limitation of the study. No patients had $BMI > 30$. Five of the 12 women were overweight ($BMI \geq 25$), and cutaneous or fat necrosis was observed in two of their flaps. In a Finnish population study, 21.6 % of women aged 30 to 64 years and 31.3 % of women aged 65 years or more had $BMI > 30$ % in 2000–2001 (Aromaa 2002). Had our study group been larger, more patients likely would have been obese, and a connection might have emerged between BMI and cutaneous necrosis.

The effect of the type of body fat distribution on development of cutaneous necrosis has not been investigated earlier in TRAM flaps. In this study, five of 12 patients developed marginal cutaneous or fat necrosis on the contralateral side of pedicled TRAM flaps. There were no flaps with necrosis in the patients with upper body type fat distribution ($WHCR > 0.84$). Upper body type (male type) obesity has been associated with cardiovascular problems (Lapidus 1984, Björntorp 1988, Kannel 1991) and increased peripheral vascular resistance (Jern 1992) in women. Increased peripheral resistance may be one contributing factor in development of partial necrosis in pedicled flaps, so one would expect necrosis to be more common in patients with upper body type fat distribution. However, the results of this study contradict this hypothesis, instead suggesting an association between lower body type (female type) fat distribution and development of marginal necrosis in pedicled TRAM flaps.

In pedicled TRAM flaps, peripheral vascular resistance might not play a major role in development of marginal cutaneous or fat necrosis. In women with lower body type fat distribution, the relative overweight in the lower abdomen likely stretches the perforators running through the rectus muscles, as suggested by Schefflan (Schefflan 1984). In such cases, the SEA cannot provide sufficient blood supply to the entire flap. One can also speculate that the flap area is too large to be perfused sufficiently in women with lower body type fat distribution. The exact size of the skin island of the TRAM

flap was not measured in this study, but the size of the TRAM flap was chosen to achieve the best possible symmetry with the other breast. Another explanation might be that the superior epigastric vessels are smaller in women with lower type body fat distribution. If this hypothesis proves to be correct, a free TRAM flap might be more suitable than a pedicled flap for breast reconstruction in women with lower body type obesity. The caliber of the superior epigastric vessels could be established preoperatively with computed tomography angiography or intraoperatively with ICG angiography, and in the case of very thin vessels, the operation plan could be changed e.g. to a free TRAM flap

The amount of obesity can be estimated also by measuring the thickness of subcutaneous fat with ultrasound (Katch 1983, Ramirez 1992, Suzuki 1993, Orphanidou 1994). Here, the mean thickness of abdominal fat increased

during the first week after the operation. It then stayed fairly unchanged throughout the nine-month study period. The initial increase of thickness probably resulted from edema in the immediate postoperative period and remodeling of the flap. Based on these findings, the thickness of abdominal fat does not seem to be associated with cutaneous necrosis of pedicled TRAM flaps. Recently, Yano and co-workers measured the thickness of abdominal subcutaneous fat preoperatively in 50 pedicled TRAM flaps. Three of their patients developed cutaneous necrosis and six fat necrosis of the flap. Their results showed that abdominal fat thickness is not a risk factor for necrosis in pedicled TRAM flaps in patients who are thin, average, or mildly obese. Their findings are in accordance with ours. They also observed a close correlation between BMI and thickness of subcutaneous fat in the abdominal area (Yano 2003).

7 Conclusions

1. During breast reconstruction with a pedicled TRAM flap, elevation of the contralateral side of the flap causes an increase in cutaneous blood flow of the flap. When the DIEA is ligated, a decrease in cutaneous blood flow is observed with LDF and $P_{tc}O_2$ on the contralateral side of the flap, continuing on the postoperative days. The LDF and $P_{tc}O_2$ levels are lower on the contralateral side than on the ipsilateral side of the flap at all measuring times (I).

In a free TRAM flap, the intraoperative changes in cutaneous blood flow are similar to those in a pedicled flap. The postoperative blood flow in a free TRAM flap measured by $P_{tc}O_2$ and LDF is more generous than in a pedicled flap (II).

2. Development of cutaneous necrosis of a pedicled TRAM flap can be predicted based on intraoperative LDF measurements. The contralateral LDF value decreases to 43 ± 7 % of the initial value after ligation of the DIEA in flaps developing cutaneous necrosis during the next week. Cutaneous necrosis cannot be predicted based on intraoperative $P_{tc}O_2$ values (I).
3. A correlation exists between the perioperative plasma ET-1 concentrations and the peripheral vasoconstriction, as well as between plasma ET-1 concentrations and MAP during and after a long plastic surgical operation. ET-1 levels are elevated in the recovery room. No association is present between ET-1 concentrations in systemic blood and development of cutaneous necrosis or HR in pedicled TRAM flaps (III).
4. Felodipine, a vasodilating calcium channel blocker, has no effect on plasma ET-1 concentrations, peripheral vasoconstriction, postoperative $P_{tc}O_2$, or development of cutaneous necrosis in free TRAM flaps. Felodipine has a minor decreasing effect on postoperative blood pressure (IV).
5. Neither BMI nor thickness of abdominal fat seems to be associated with the development of cutaneous or fat necrosis in pedicled TRAM flaps. However, this study included no patients with BMI >30. An association may exist between lower body type fat distribution and development of marginal necrosis in pedicled TRAM flaps (V).

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